Antimicrobial Drugs

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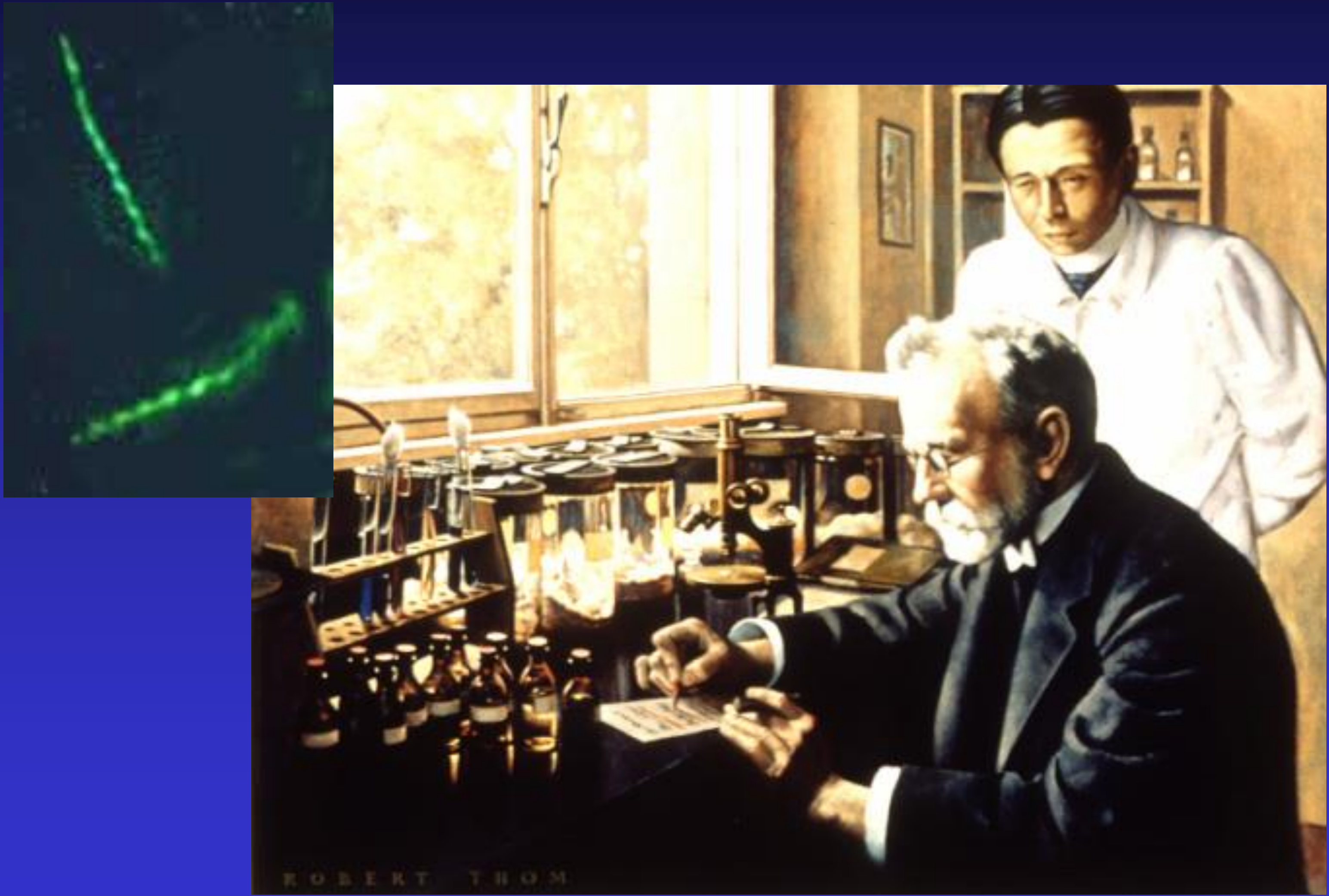
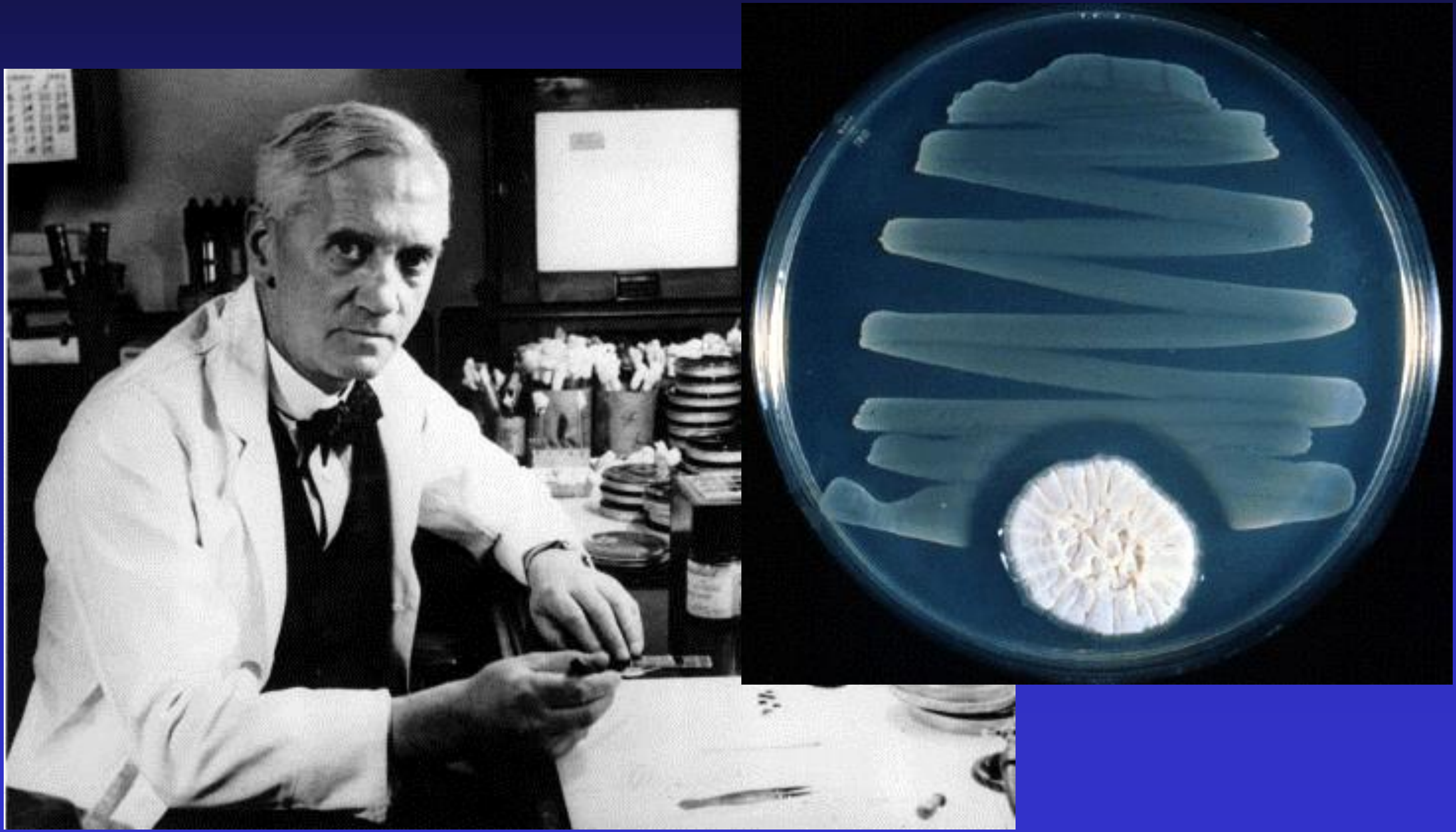
Ehrlich’s Magic Bullets



Fleming and Penicillin



Chemotherapy

- The use of drugs to treat a disease
- **Selective toxicity**: A drug that kills harmful microbes without damaging the host

Antibiotic/Antimicrobial

- Antibiotic: Chemical produced by a microorganism that kills or inhibits the growth of another microorganism
- Bacteriocide
- Bacteriostatic

- **Synergism**
- **Antagonism**

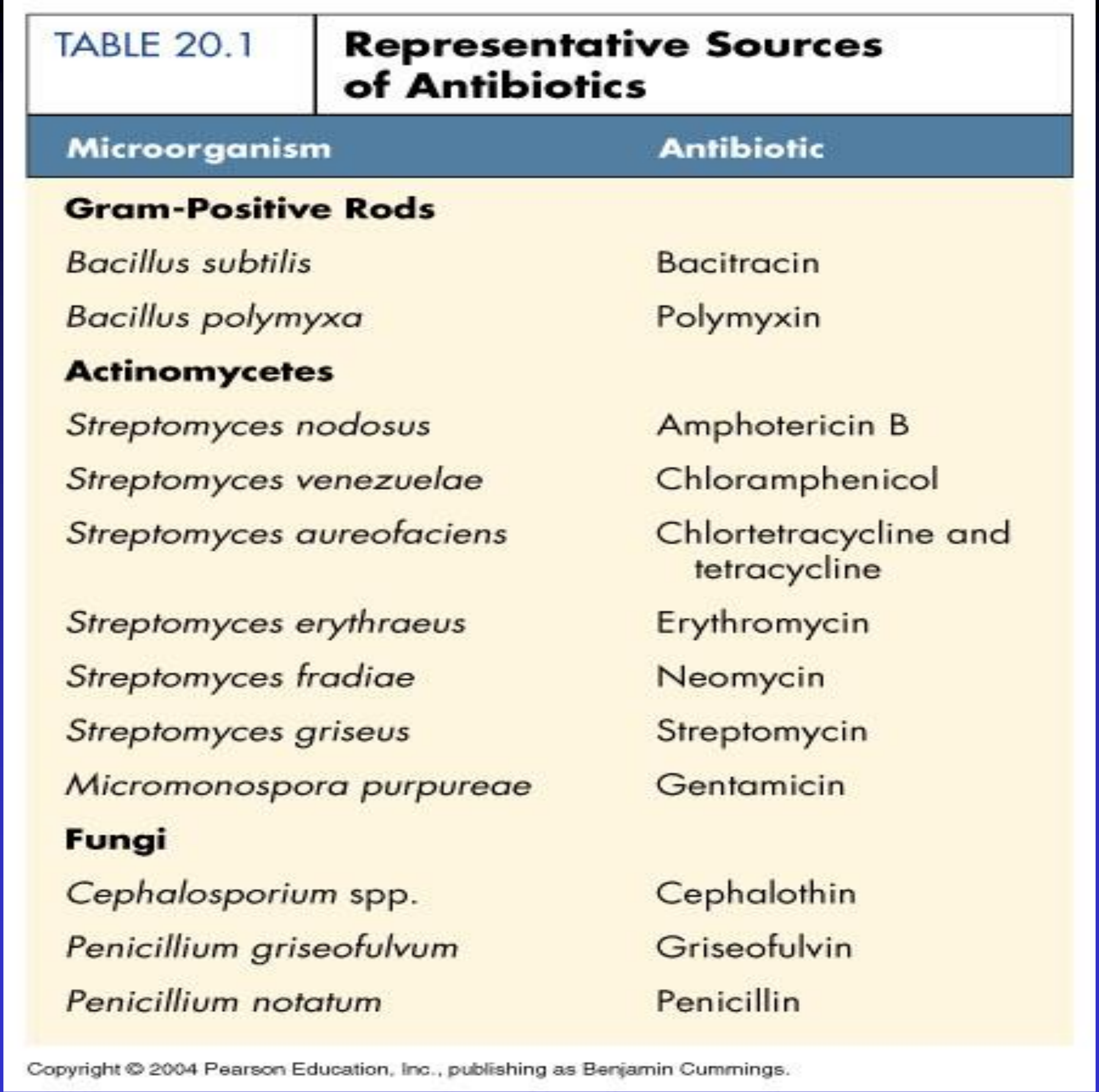


TABLE 20.1 **Representative Sources of Antibiotics**

Microorganism	Antibiotic
Gram-Positive Rods	
Bacillus subtilis	Bacitracin
Bacillus polymyxa	Polymyxin
Actinomycetes	
Streptomyces nodosus	Amphotericin B
Streptomyces venezuelae	Chloramphenicol
Streptomyces aureofaciens	Chlortetracycline and tetracycline
Streptomyces erythraeus	Erythromycin
Streptomyces fradiae	Neomycin
Streptomyces griseus	Streptomycin
Micromonospora purpureae	Gentamicin
Fungi	
Cephalosporium spp.	Cephalothin
Penicillium griseofulvum	Griseofulvin
Penicillium notatum	Penicillin

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Antibiotic Spectrum of Activity

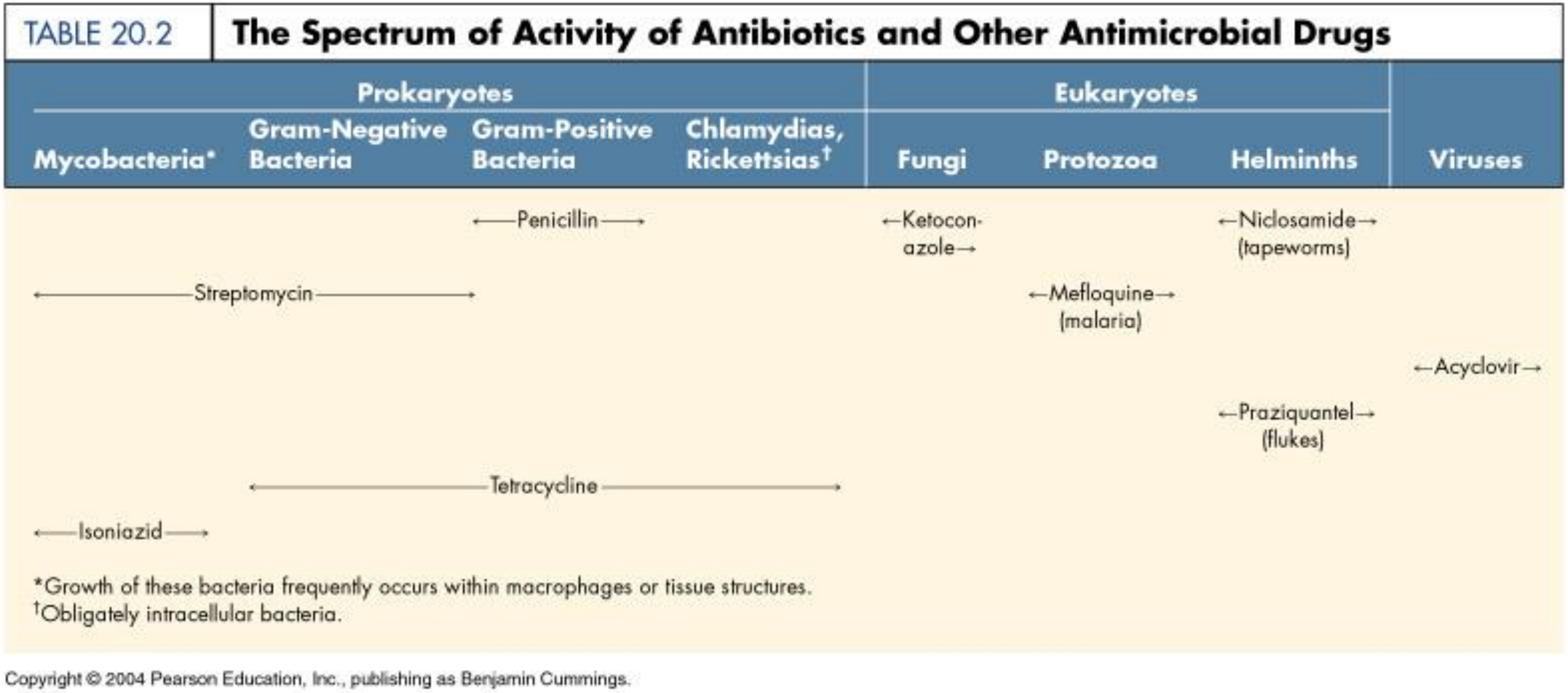

TABLE 20.2 The Spectrum of Activity of Antibiotics and Other Antimicrobial Drugs

Prokaryotes				Eukaryotes			
Mycobacteria*	Gram-Negative Bacteria	Gram-Positive Bacteria	Chlamydias, Rickettsias†	Fungi	Protozoa	Helminths	Viruses
		←Penicillin→		←Ketoconazole→		←Niclosamide→ (tapeworms)	
←Streptomycin	→				←Mefloquine→ (malaria)		
							←Acyclovir→
						←Praziquantel→ (flukes)	
	←	Tetracycline	→				
←Isoniazid→							

*Growth of these bacteria frequently occurs within macrophages or tissue structures.
†Obligately intracellular bacteria.

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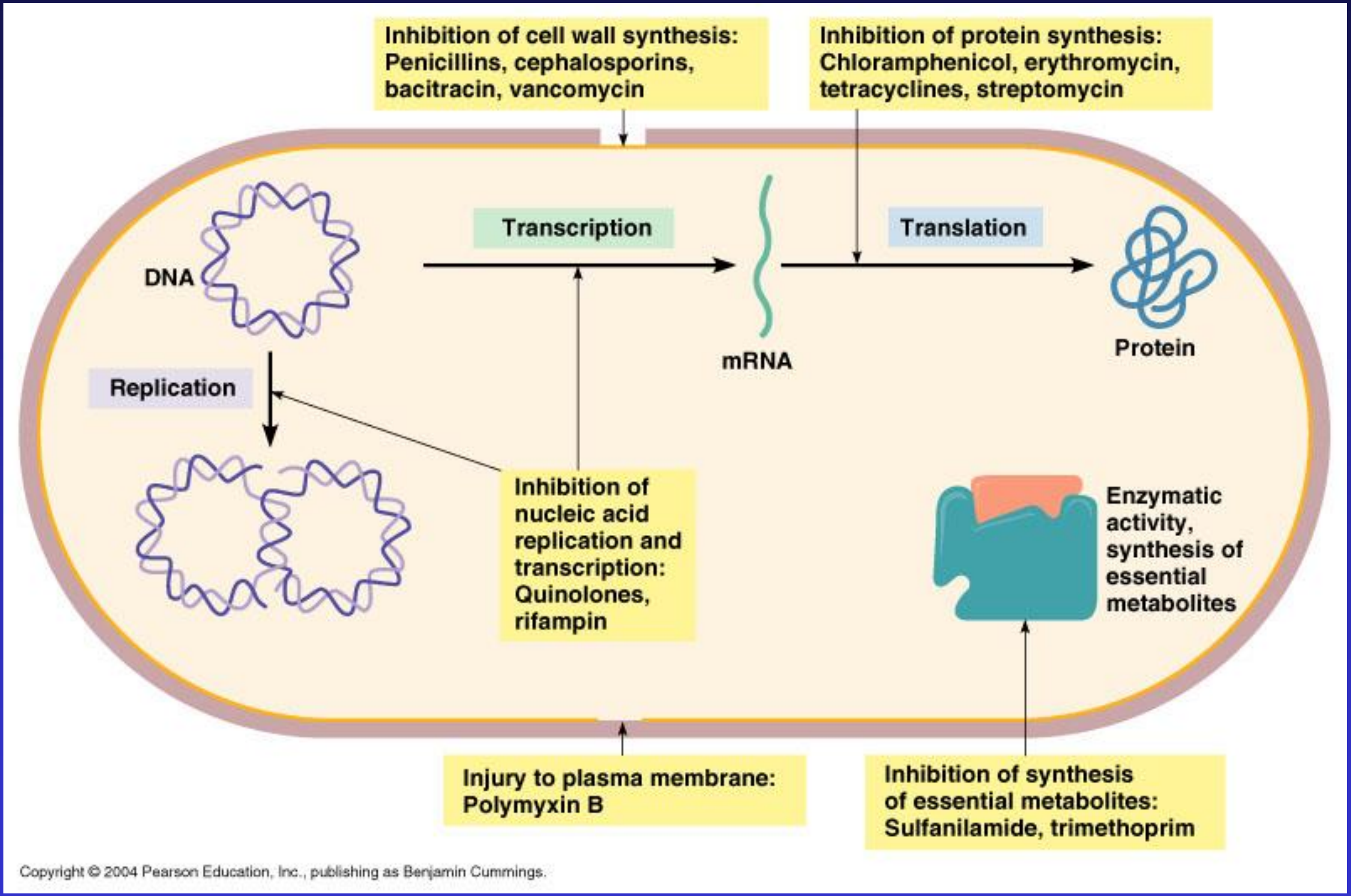
- No antibiotic is effective against all microbes

Mechanisms of Antimicrobial Action

- Bacteria have their own enzymes for
  - Cell wall formation
  - Protein synthesis
  - DNA replication
  - RNA synthesis

Modes of Antimicrobial Action



Inhibition of cell wall synthesis: Penicillins, cephalosporins, bacitracin, vancomycin

Inhibition of protein synthesis: Chloramphenicol, erythromycin, tetracyclines, streptomycin

Inhibition of nucleic acid replication and transcription: Quinolones, rifampin

Injury to plasma membrane: Polymyxin B

Inhibition of synthesis of essential metabolites: Sulfanilamide, trimethoprim

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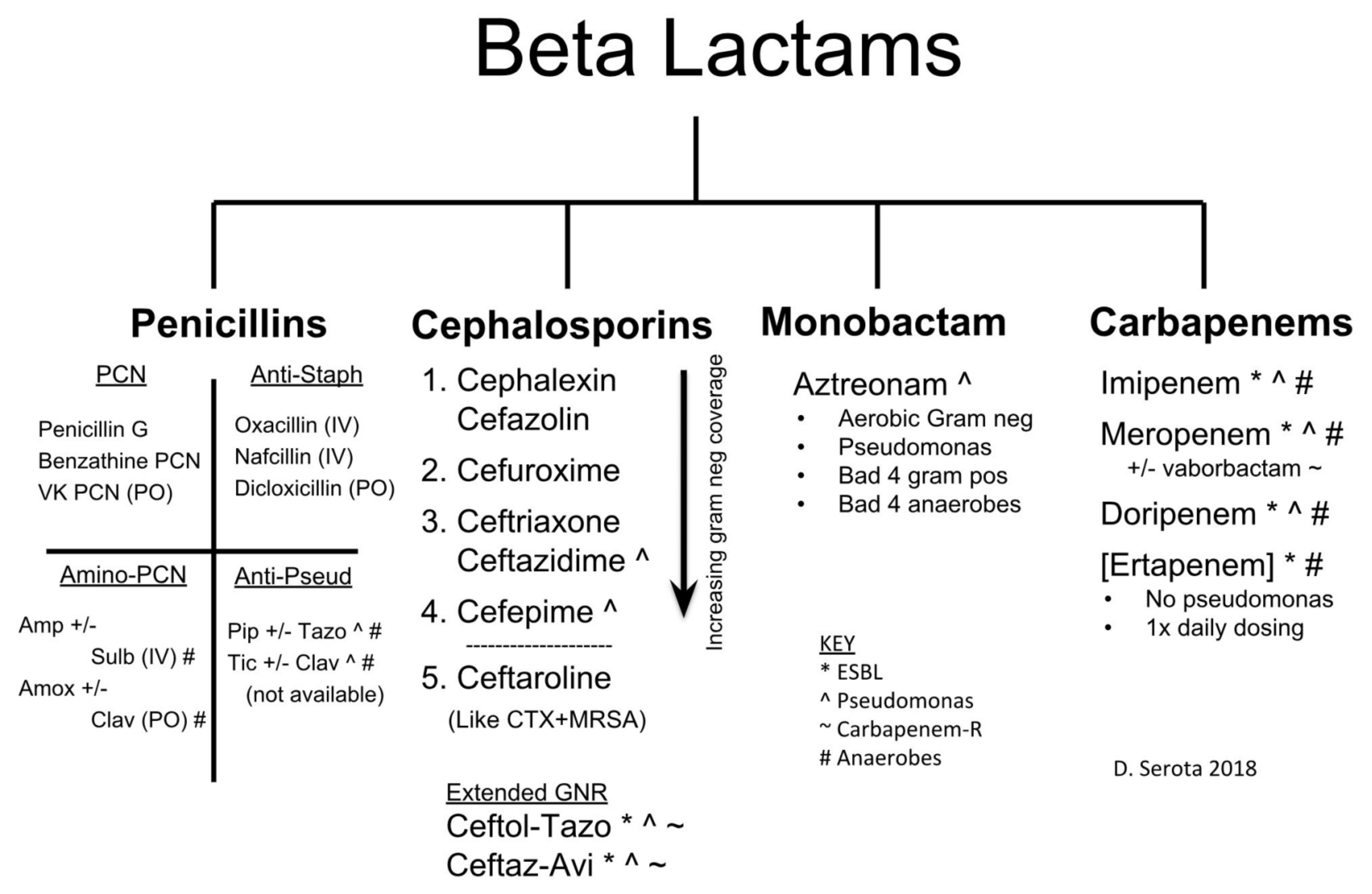
Inhibitors of Cell Wall Synthesis



Beta Lactams

Penicillins

PCN	Anti-Staph
Penicillin G Benzathine PCN VK PCN (PO)	Oxacillin (IV) Nafcillin (IV) Dicloxicillin (PO)
Amino-PCN	**Anti-Pseud**
Amp +/- Sulb (IV) # Amox +/- Clav (PO) #	Pip +/- Tazo ^ # Tic +/- Clav ^ # (not available)

Cephalosporins

1. Cephalexin
   Cefazolin
2. Cefuroxime
3. Ceftriaxone
   Ceftazidime ^
4. Cefepime ^

----

5. Ceftaroline
   (Like CTX+MRSA)

Extended GNR

Ceftol-Tazo * ^ ~

Ceftaz-Avi * ^ ~

Monobactam

Aztreonam ^

- Aerobic Gram neg
- Pseudomonas
- Bad 4 gram pos
- Bad 4 anaerobes

KEY

* ESBL

^ Pseudomonas

~ Carbapenem-R

Anaerobes

Carbapenems

Imipenem * ^ #

Meropenem * ^ #
+/- vaborbactam ~

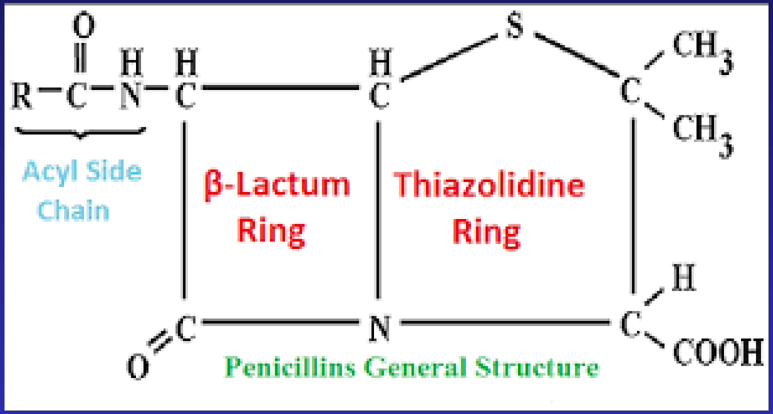
Doripenem * ^ #

[Ertapenem] * #

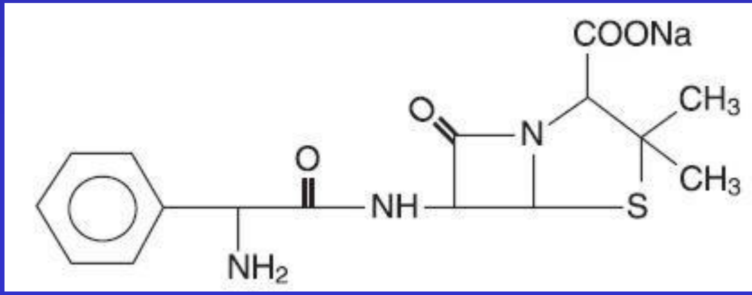
- No pseudomonas
- 1x daily dosing

D. Serota 2018

Inhibitors of Cell Wall Synthesis

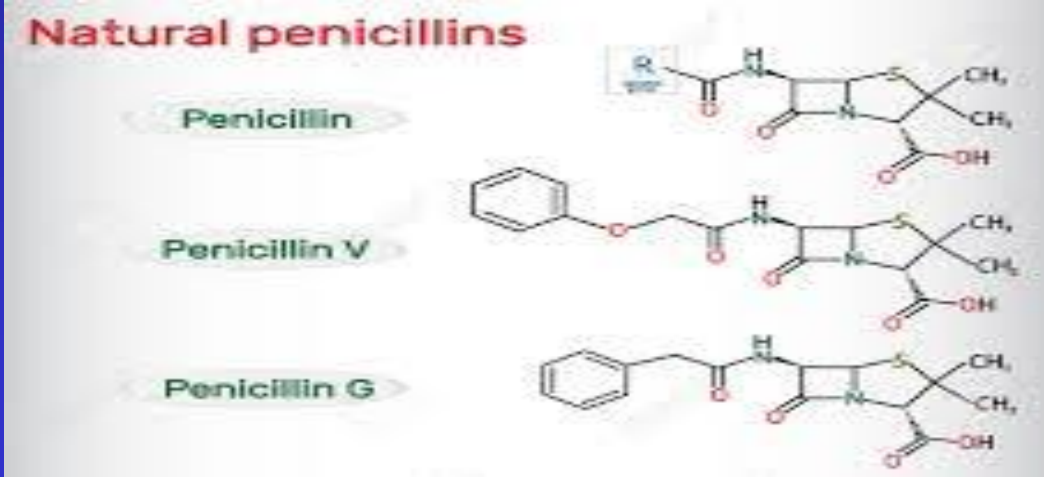


- Beta-lactams antibiotics
- Penicillin
- Natural penicillins
  - Narrow range of action
  - Susceptible to penicillinase (β lactamase)
- 6-aminopenicillanic acid:
  - 4-sided ring (β lactam ring)
  - Thiazolidine ring

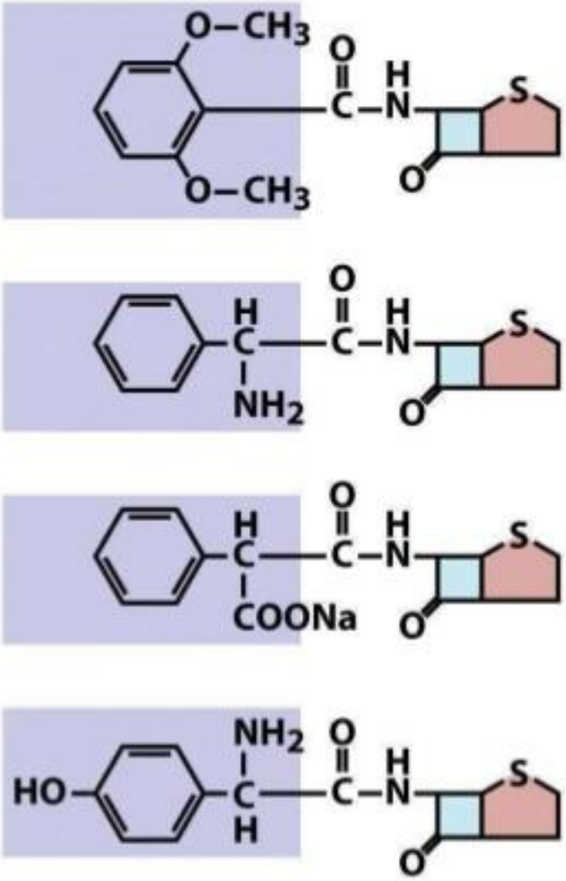


Natural Pen.

- Penicillin G is a natural penicillin that is produced directly from fermentation of *Penicillium*.
- It is a natural penicillin antibiotic that is administered intravenously or intramuscularly due to poor oral absorption.
- Penicillin V is a derivative of penicillin G and because of similarities in spectrum of activity, is considered a natural penicillin.



Semisynthetic penicillins



Methicillin
(penicillinase resistant)

Ampicillin
(broad spectrum, acid resistant)

Carbenicillin
(broad spectrum)

Amoxicillin
(broad spectrum)

- **Antistaphylococcal penicillins(stable to staphylococcapl -lactamase) or** Penicilinase-resistant penicillins

  Methicillin. Cloxacillin, Flucloxacillin, Oxacillin, Dicloxacillin, Nafcillin

- **Penicillins with activity against enterobacteria (**Extended-spectrum penicillins)

Aminopenicillins : (Ampicillin (and esters) and Amoxycillin) and Mecillinam, Cyclacillin, Epicillin

- **Penicillins that are stable to enterobacterial beta-lactamases“**

  Temocillin,

- **Penicillins with activity against Pseudomonas aeruginosa**

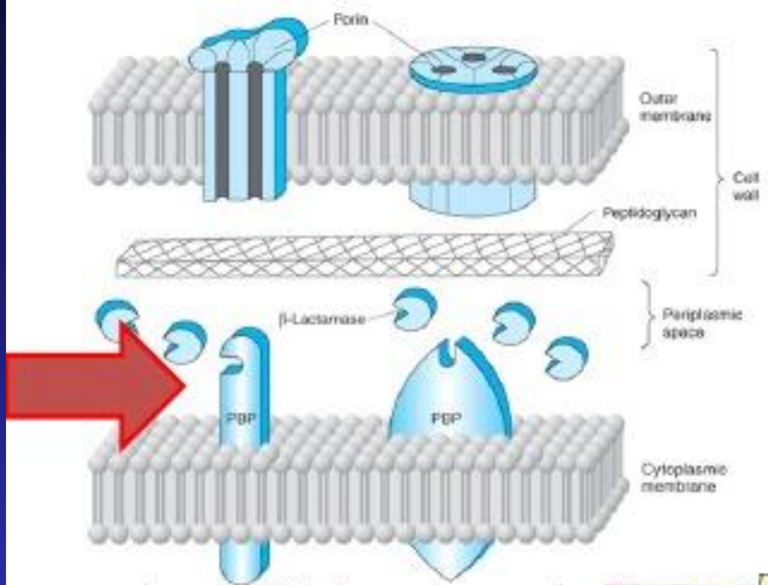
  Carbenicillin, Ticarcillin, Azlocillin, Mezlocillin, Piperacillin

- **Penicillins + β-lactamase inhibitors:**

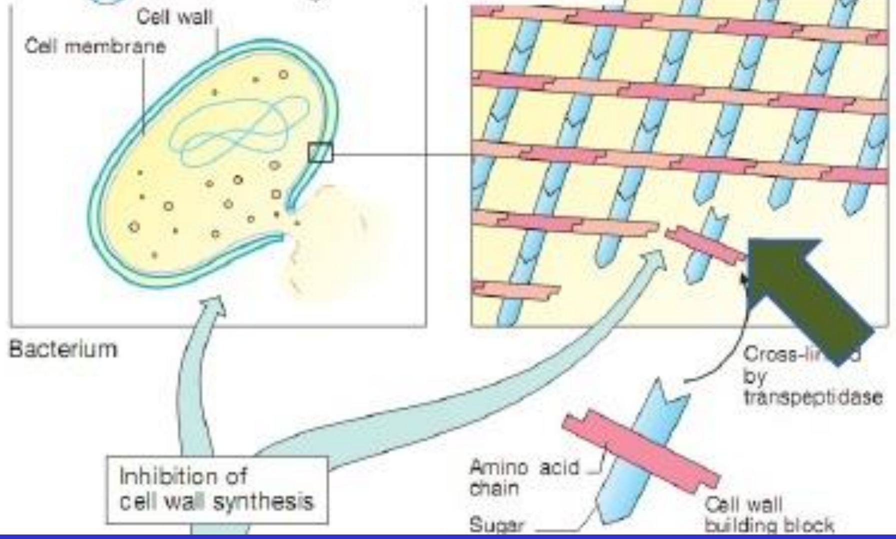
  β-*lactamase inhibitors* (acid clavulanic, sulbactam, and *tazobactam*)

Amoxicillin/clavulanic acid, also known as co-amoxiclav,

Mechanism of action 1

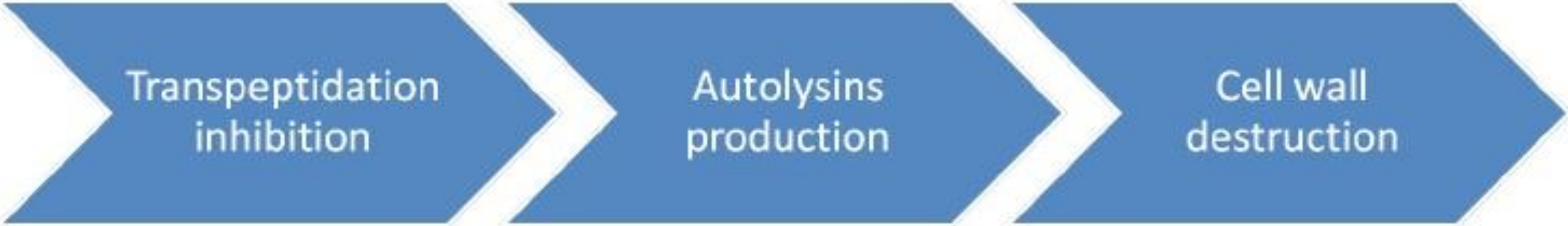


- Beta-lactams bind PBP (Penicillin Binding Proteins).



- Some PBP have transpeptidase activity.
- Transpeptidase activity is essential in cell wall synthesis.

Mechanism of action 2



Transpeptidation inhibition

Autolysins production

Cell wall destruction

long-acting salts

- The long-acting salts of penicillin are poorly soluble depot preparations that are injected intramuscularly and release benzylpenicillin (penicillin G) slowly from the injection site.
- **Procaine benzylpenicillin (INN), also known as procaine G penicillin**, is an injectable antiobiotic.
- It is a poorly soluble salt form of penicillin + **local anaesthetic** agent procaine.
- And can maintain a concentration of penicillin inhibitory to many sensitive organisms for up to 24 h.

- benzathine and benethamine penicillin

Benzathine and benethamine penicillin are even less soluble and liberate small amounts of penicillin over several days

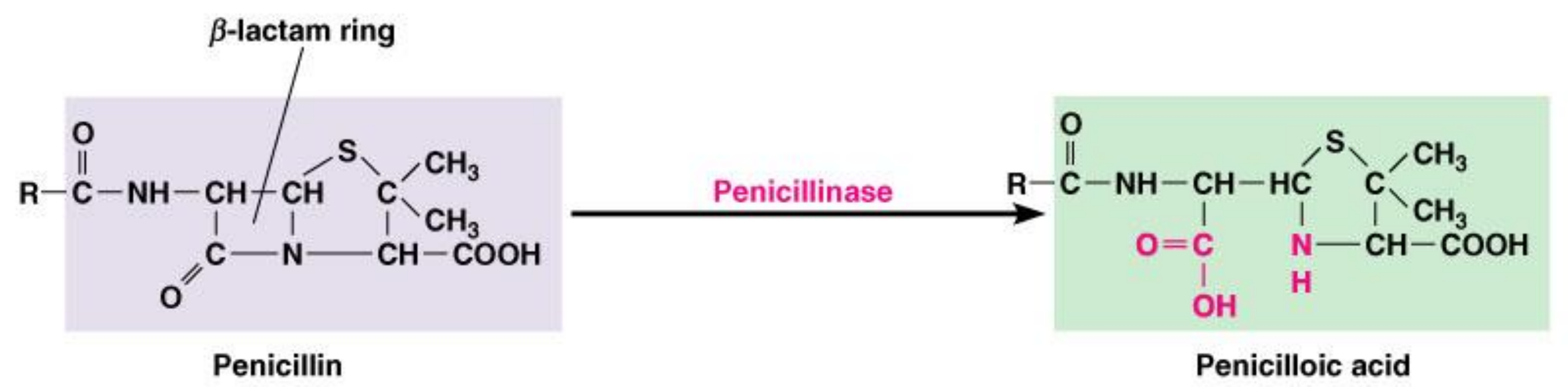
- Probenecid

Probenecid also inhibits the excretion of penicillin in renal tubular and has been used as an assistant to penicillin therapy to increase plasma drug levels

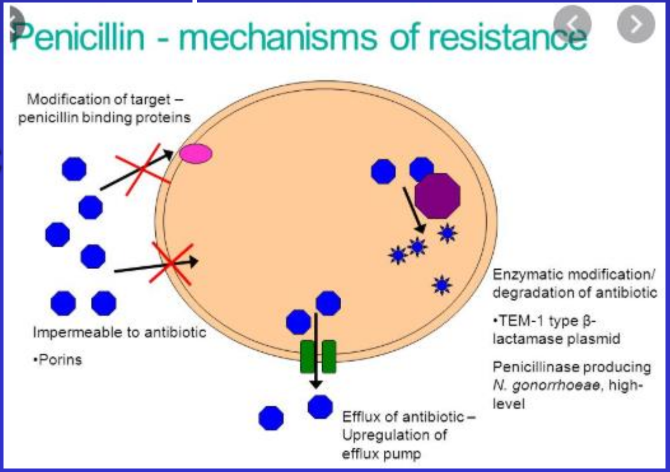
- Penicillin G potassium and sodium salts

Resistance mechansims

- **Produce beta-lactamase (penicillinase)**
  - **destroys antibiotic**
  - some Enterobacteriaceae can produce enzymes called extended-spectrum beta-lactamases (ESBLs). ESBL enzymes break down and destroy some commonly used antibiotics, including penicillins and cephalosporins.

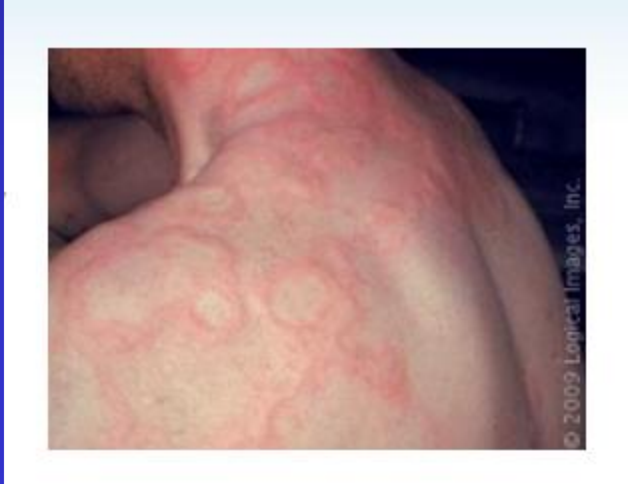


- **modified penicillin binding proteins (PBP)**
  - **don’t bind antibiotic**
  - The antibacterial targets of β-lactam antibiotics are the PBPs.
  - For ex.: *S. aureus* expressing four native PBPs (PBP1, PBP2, PBP3, and PBP4). In addition to these four PBPs, MRSA also expresses a fifth PBP (PBP2A) which, unlike the native *S. aureus* PBPs, is a poor target for the β-lactam.
- **modified porins**
  - **no internalization of antibiotic**


Penicillin - mechanisms of resistance
Modification of target – penicillin binding proteins
Impermeable to antibiotic
•Porins
Enzymatic modification/ degradation of antibiotic
•TEM-1 type β-lactamase plasmid
Penicillinase producing *N. gonorrhoeae*, high-level
Efflux of antibiotic – Upregulation of efflux pump

Penicillin allergy

- range from a rash to anaphylaxis, a potentially life-threatening condition.
- severe skin rash, itching, hives difficulty breathing or swallowing



- responsible antigens are degradation products (eg, penicilloic acid) bound to host protein.
- Skin tests with penicilloyl-polylysine or with alkaline hydrolysis products identify many hypersensitive persons

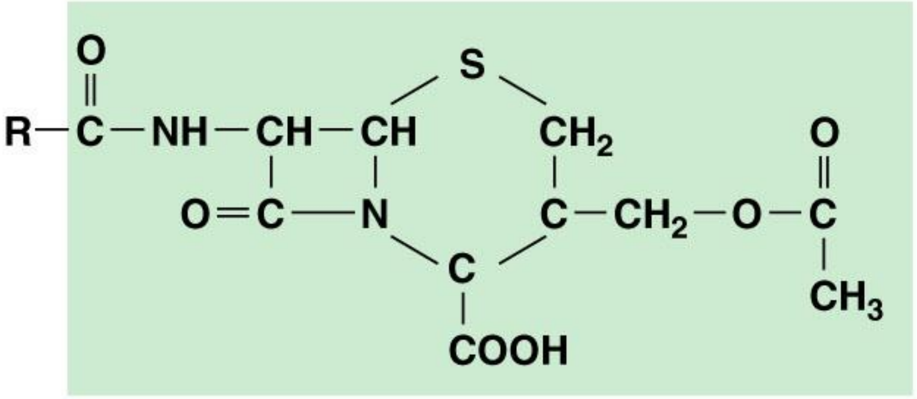
Other Inhibitors of Cell Wall Synthesis

- Cephalosporins
  - 1th, 2nd, 3rd, and 4th

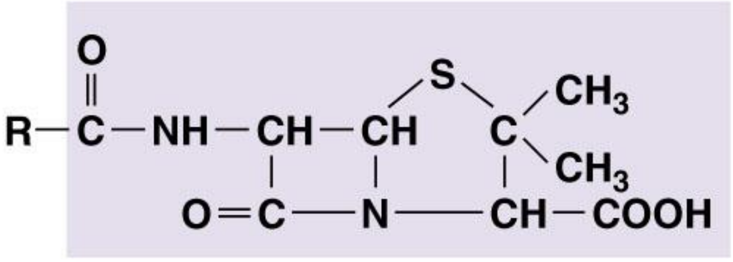
7aminocephalosporonic acid extracted from Cephalosporium *acromonium* :

Beta-lactam

Dihydrothiazine

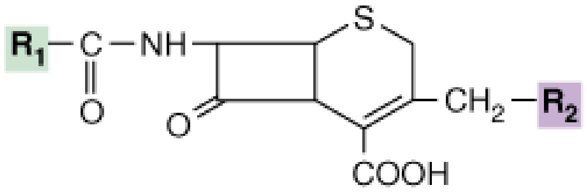


Cephalosporin nucleus

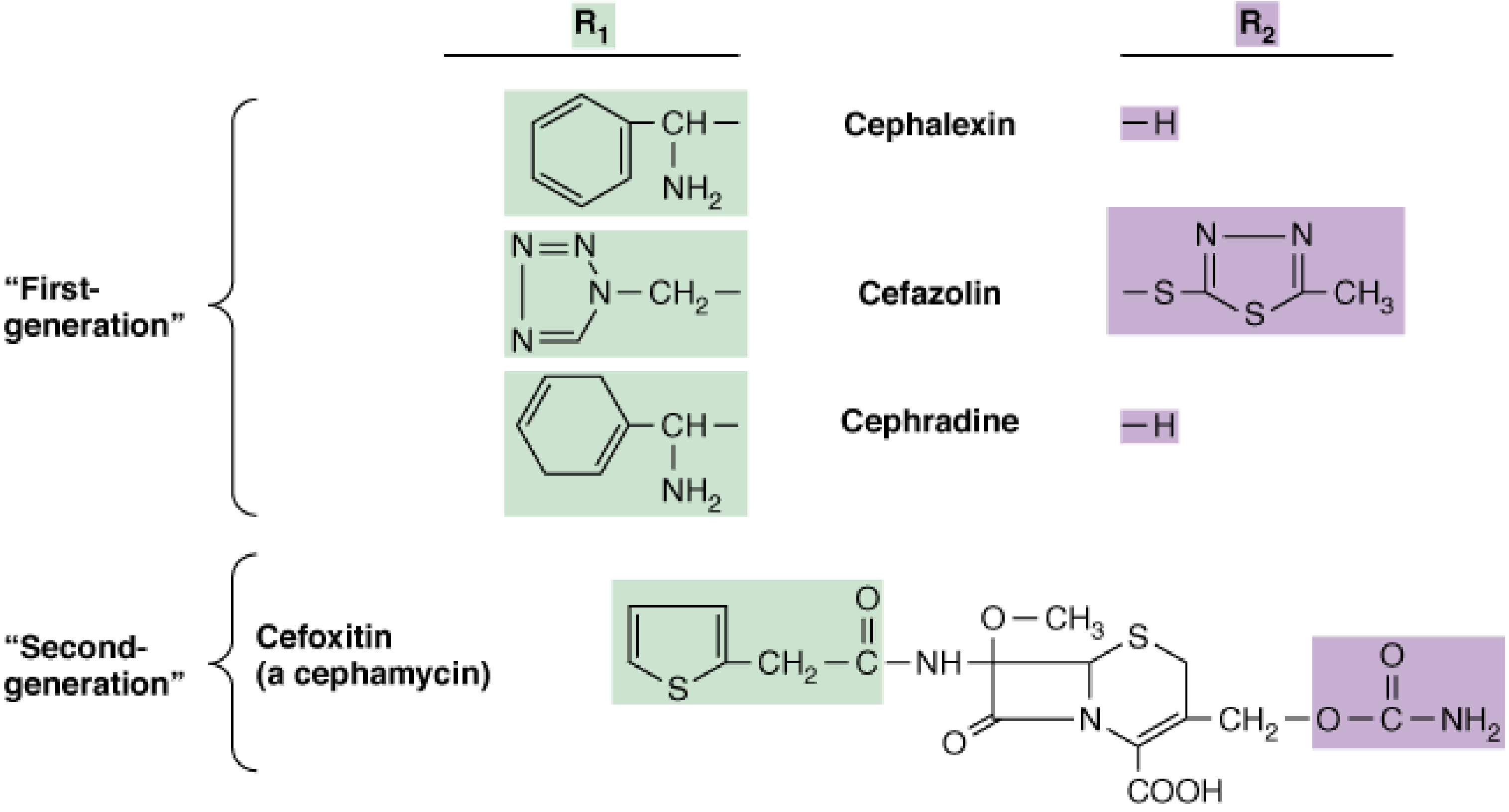


Penicillin nucleus

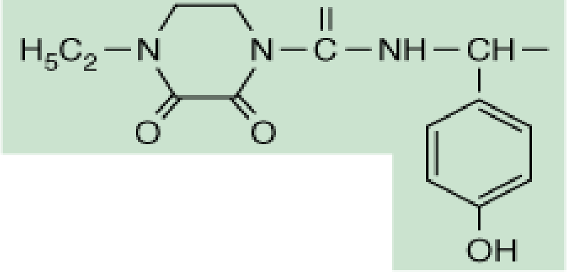
Figure 20.9



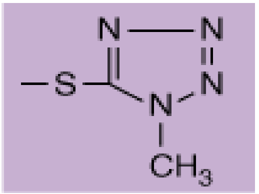
7-Aminocephalosporanic acid nucleus. The following structures can each be substituted at R_1 and R_2 to produce the named derivatives.

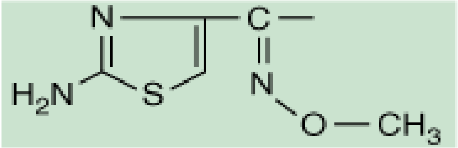


"Third-generation"

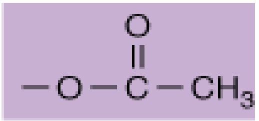


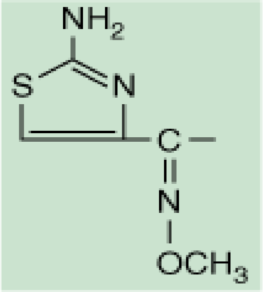
Cefoperazone



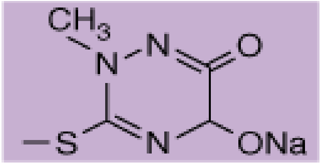


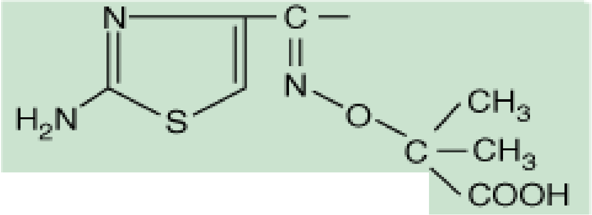
Cefotaxime



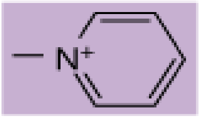


Ceftriaxone

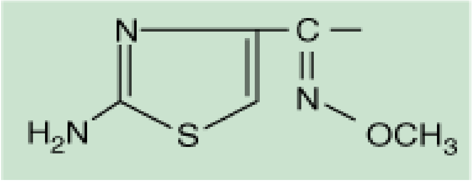




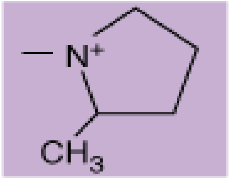
Ceftazidime

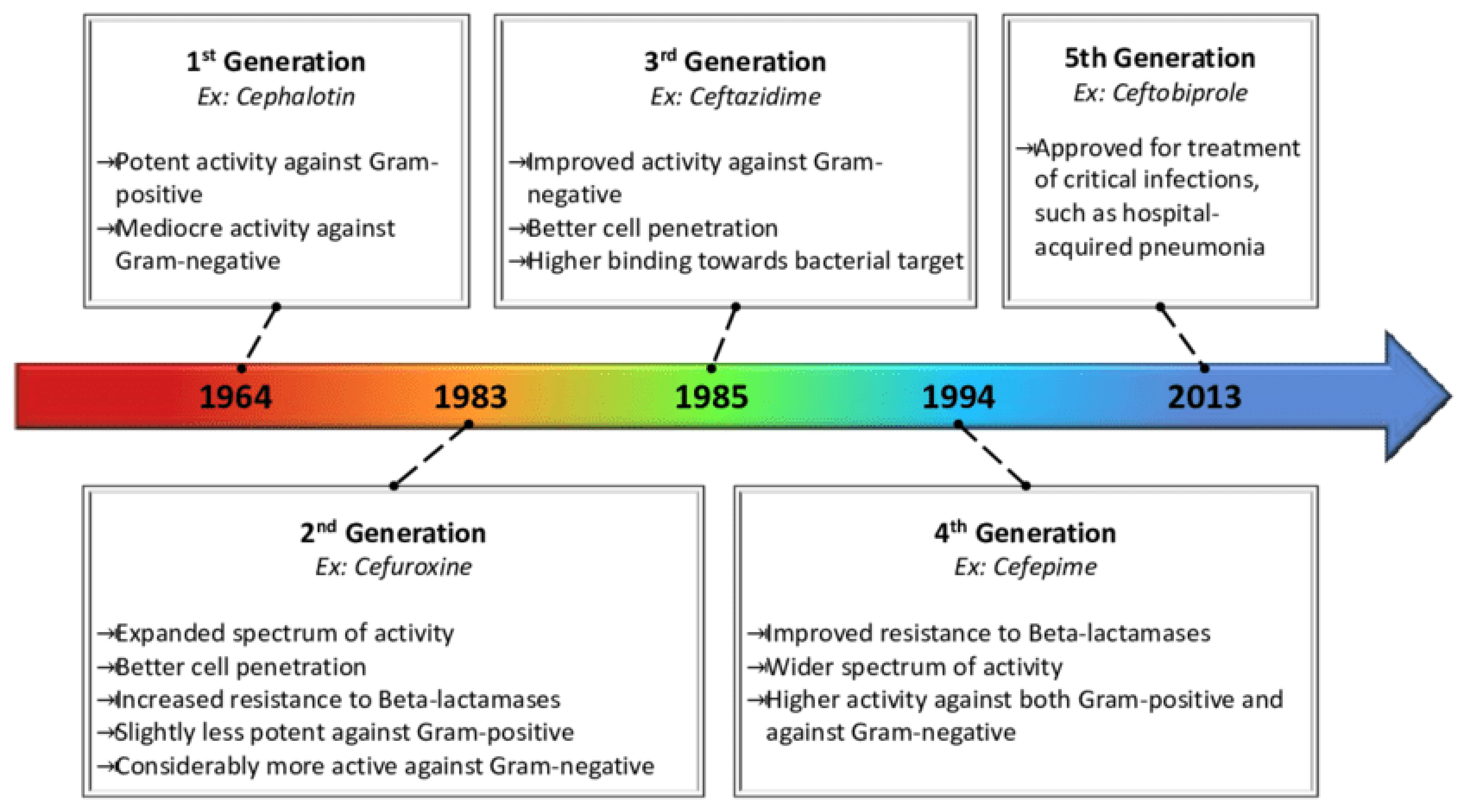


"Fourth-generation"



Cefepime





1964

1st Generation

Ex: Cephalotin

- →Potent activity against Gram-positive
- →Mediocre activity against Gram-negative

1983

2nd Generation

Ex: Cefuroxine

- →Expanded spectrum of activity
- →Better cell penetration
- →Increased resistance to Beta-lactamases
- →Slightly less potent against Gram-positive
- →Considerably more active against Gram-negative

1985

3rd Generation

Ex: Ceftazidime

- →Improved activity against Gram-negative
- →Better cell penetration
- →Higher binding towards bacterial target

1994

4th Generation

Ex: Cefepime

- →Improved resistance to Beta-lactamases
- →Wider spectrum of activity
- →Higher activity against both Gram-positive and against Gram-negative

2013

5th Generation

Ex: Ceftobiprole

- →Approved for treatment of critical infections, such as hospital-acquired pneumonia

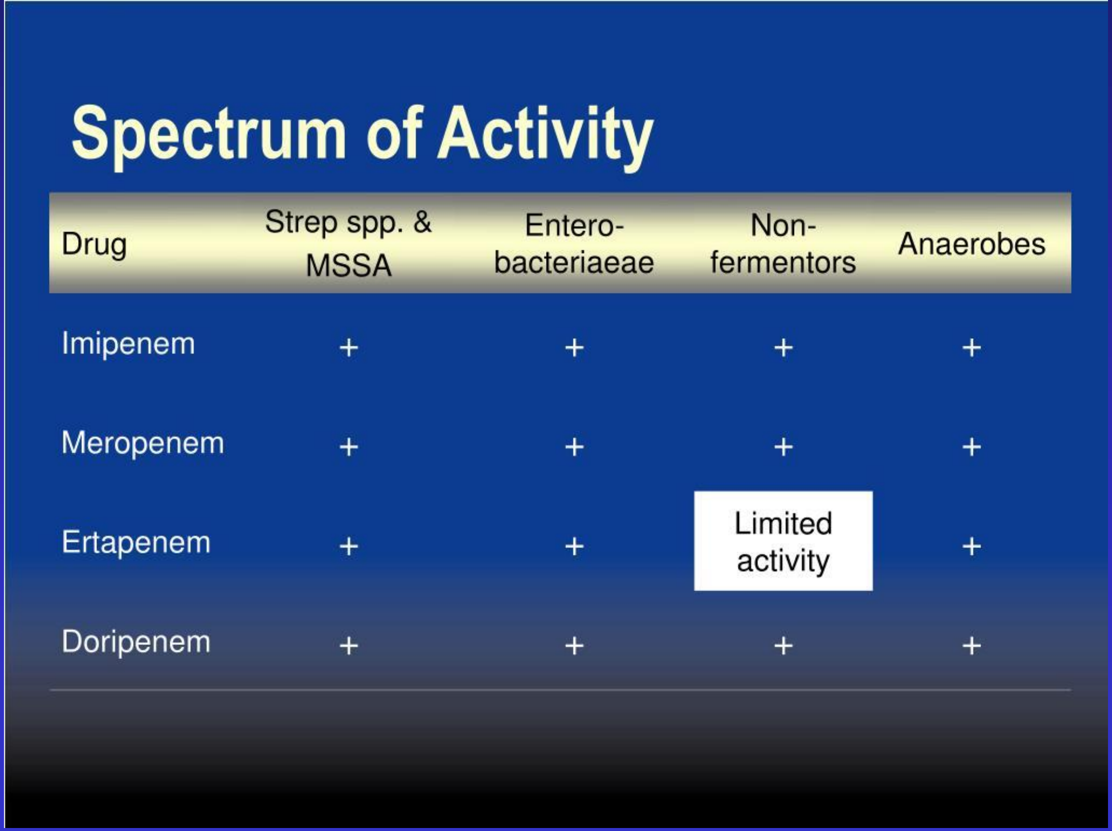
Fifth generation

- **Ceftaroline** has higher affinity for PBP2a in methicillin-resistant staphylococci, and has activity against MRSA, as well as vancomycin-intermediate *Staphylococcus aureus* (VISA).
- In addition, ceftaroline has activity for *S. pneumoniae* that is intermediate or resistant to penicillin or ceftriaxone.

Other penicillin-like antibiotics

- Carbapenem:

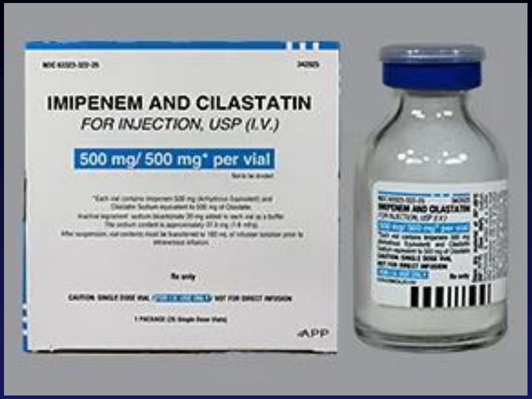
Imipenem and meropenem



Spectrum of Activity

Drug	Strep spp. & MSSA	Entero-bacteriaeae	Non-fermentors	Anaerobes
Imipenem	+	+	+	+
Meropenem	+	+	+	+
Ertapenem	+	+	Limited activity	+
Doripenem	+	+	+	+

Carbapenem

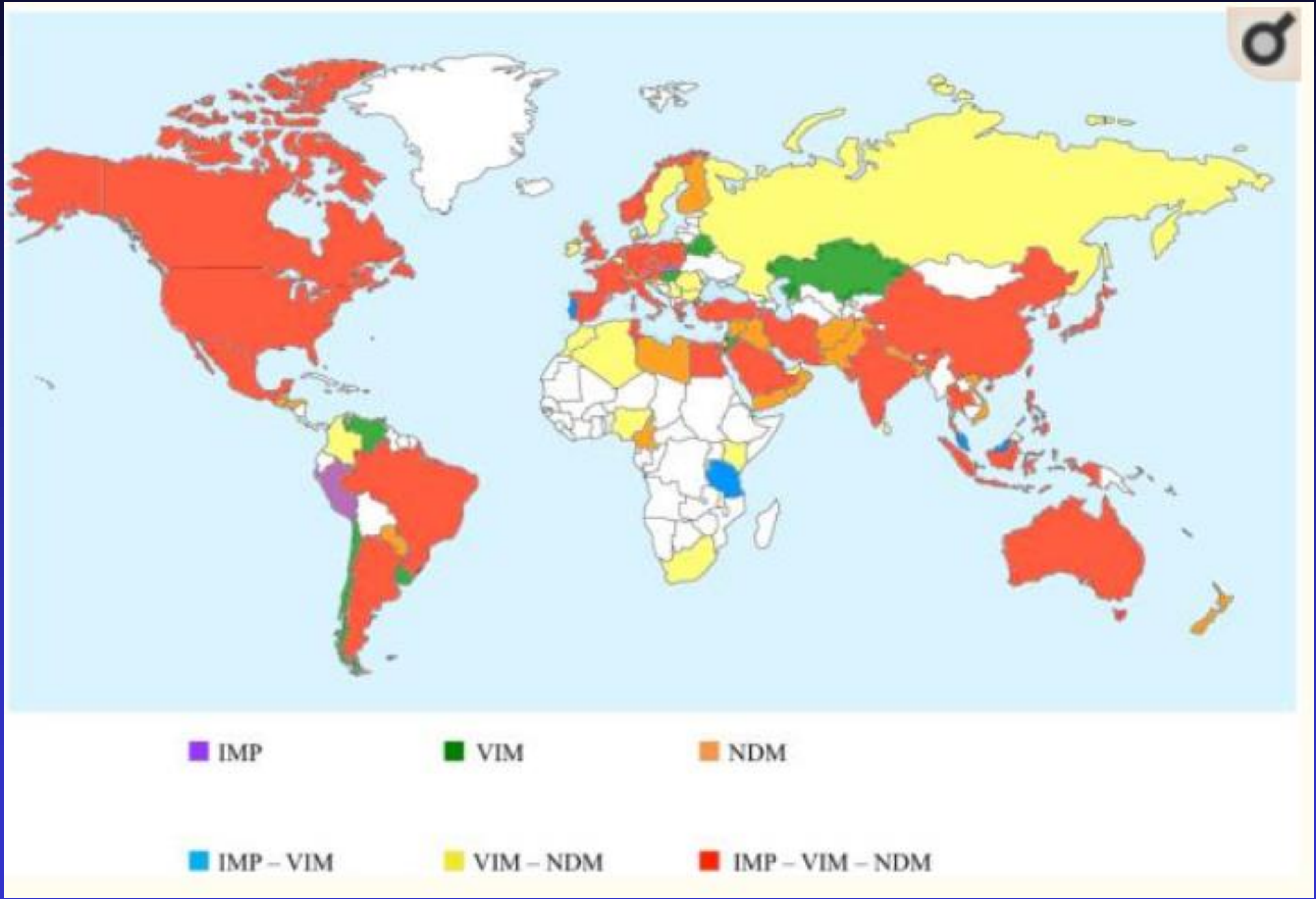


- Mechanism:
- Specifically inhibits PBP-1 , 2.
- Carbapenems are one of the few remaining antibiotics that can treat ESBL-producing germs, but resistance enzymes that destroy these antibiotics are on the rise, too.
- Resistance:

Methalobetallactamase (MBL) = NDM-1, IMP-1 and VIM-2

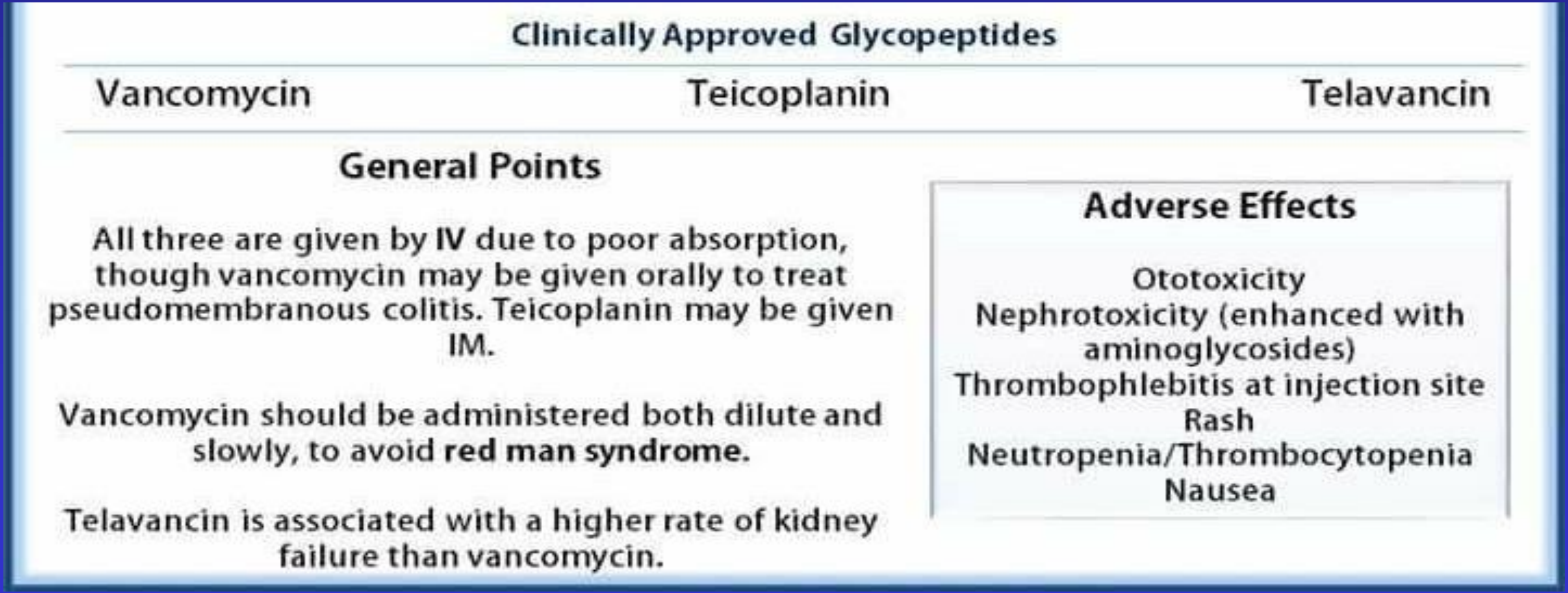
Klebsiella pneumoniae **carbapenemases** (KPCs) are plasmid encoded carbapenem hydrolyzing **enzymes.**

Cilastatin ???


IMP
VIM
NDM
IMP – VIM
VIM – NDM
IMP – VIM – NDM

Glycopeptides

- too large
- Glycopeptides are considered antibiotics of last resort for the treatment of life-threatening infections caused by relevant Gram-positive human pathogens, such as *Staphylococcus aureus*, *Enterococcus* spp. and *Clostridium difficile*.



Clinically Approved Glycopeptides

Vancomycin	Teicoplanin	Telavancin

General Points

All three are given by IV due to poor absorption, though vancomycin may be given orally to treat pseudomembranous colitis. Teicoplanin may be given IM.

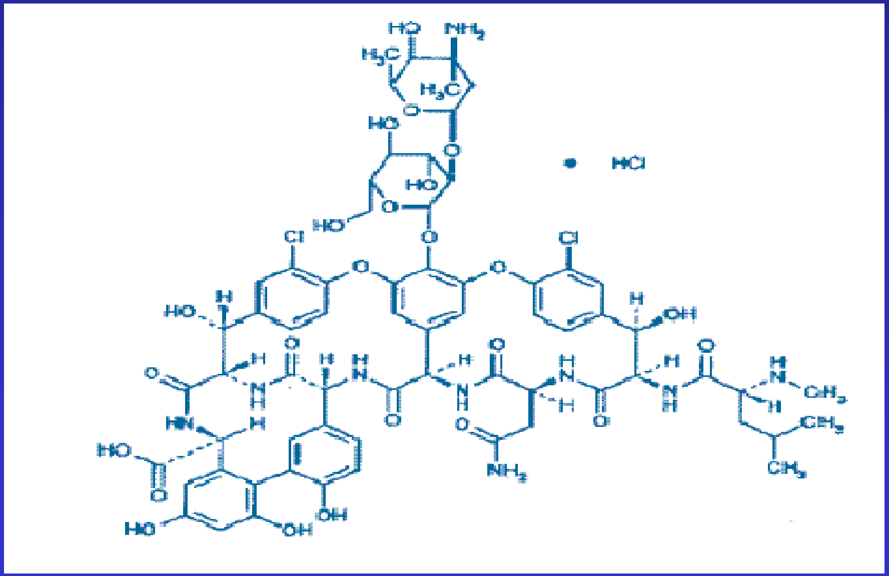
Vancomycin should be administered both dilute and slowly, to avoid **red man syndrome.**

Telavancin is associated with a higher rate of kidney failure than vancomycin.

Adverse Effects

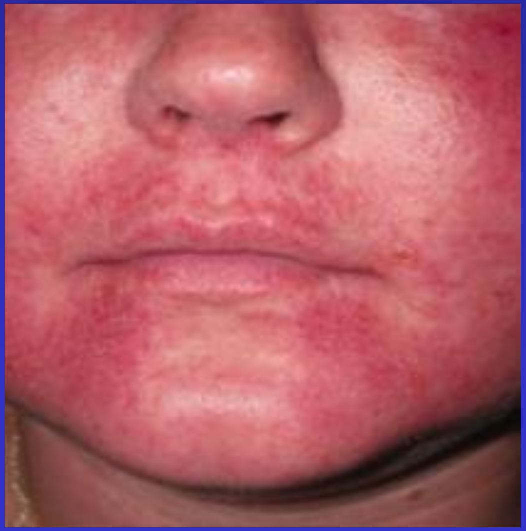
Ototoxicity
Nephrotoxicity (enhanced with aminoglycosides)
Thrombophlebitis at injection site
Rash
Neutropenia/Thrombocytopenia
Nausea

- The molecule is too large to penetrate the outer membrane of gram-negative bacilli, although some gram-negative anaerobic bacilli are anomalously sensitive

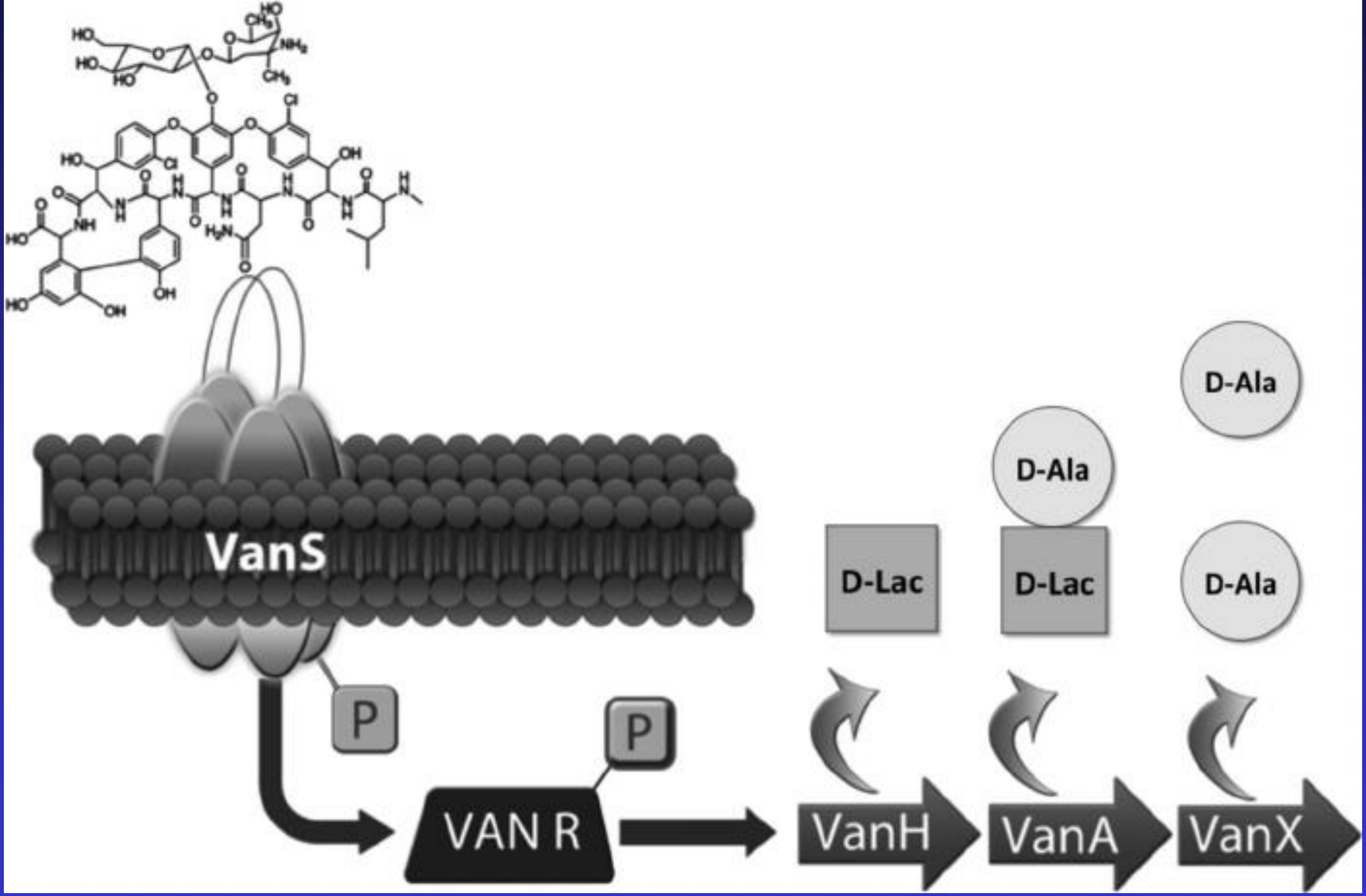


Toxicity

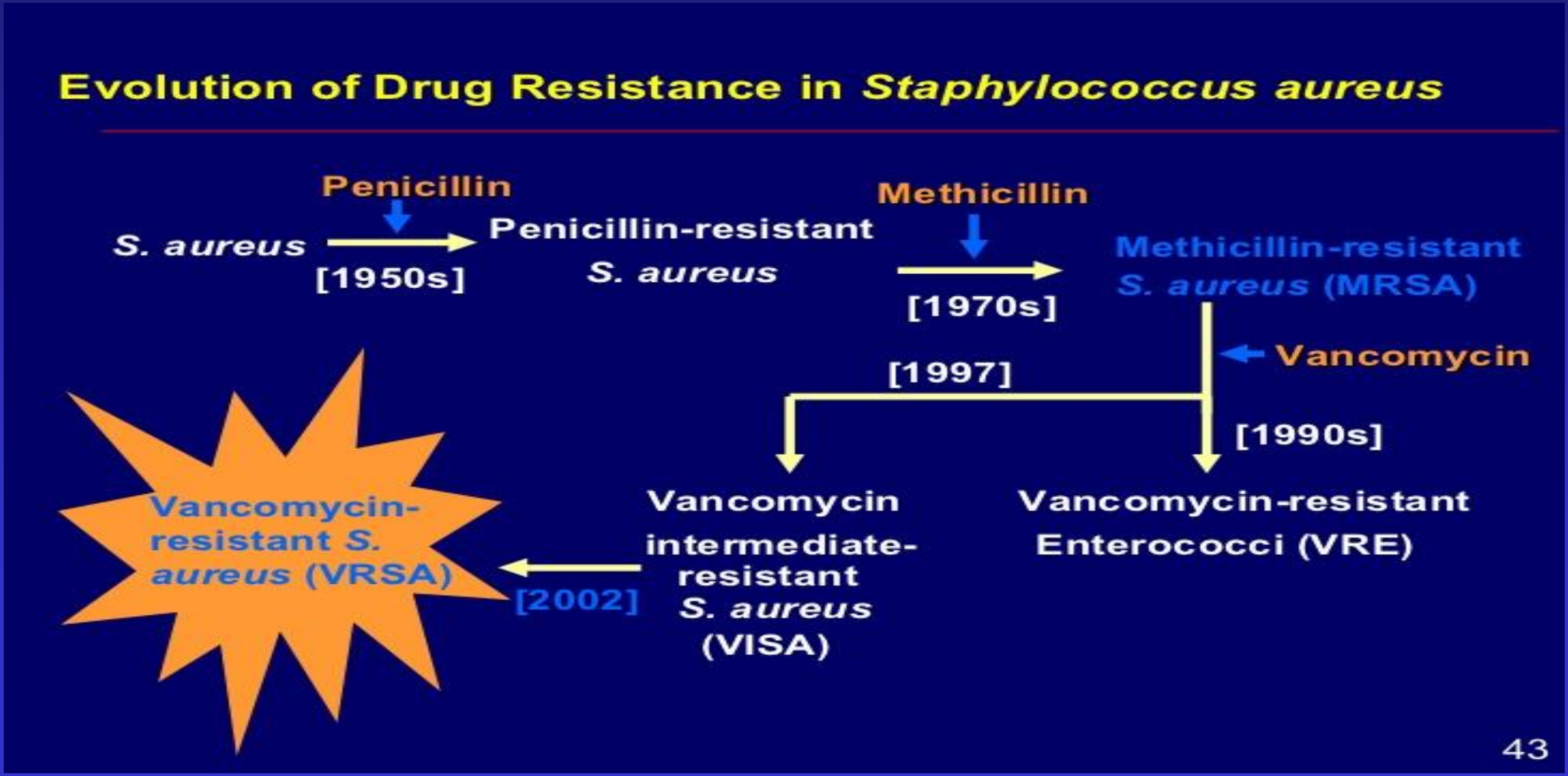
- Vancomycin has to be administered by slow intravenous infusion,
- **'red-man syndrome**' owing to the release of histamine



Resistance to Vancomycin



- Vancomycin remains one of the first-line drugs for the treatment of MRSA infections.
- However, S. aureus isolates with complete resistance to vancomycin have emerged in recent years.
- Vancomycin-resistant S. aureus (VRSA) is mediated by a **vanA gene cluster**, which is transferred from vancomycin-resistant enterococcus.



Evolution of Drug Resistance in *Staphylococcus aureus*

Penicillin

S. aureus

[1950s]

Penicillin-resistant *S. aureus*

Methicillin

[1970s]

Methicillin-resistant *S. aureus* (MRSA)

Vancomycin

[1997]

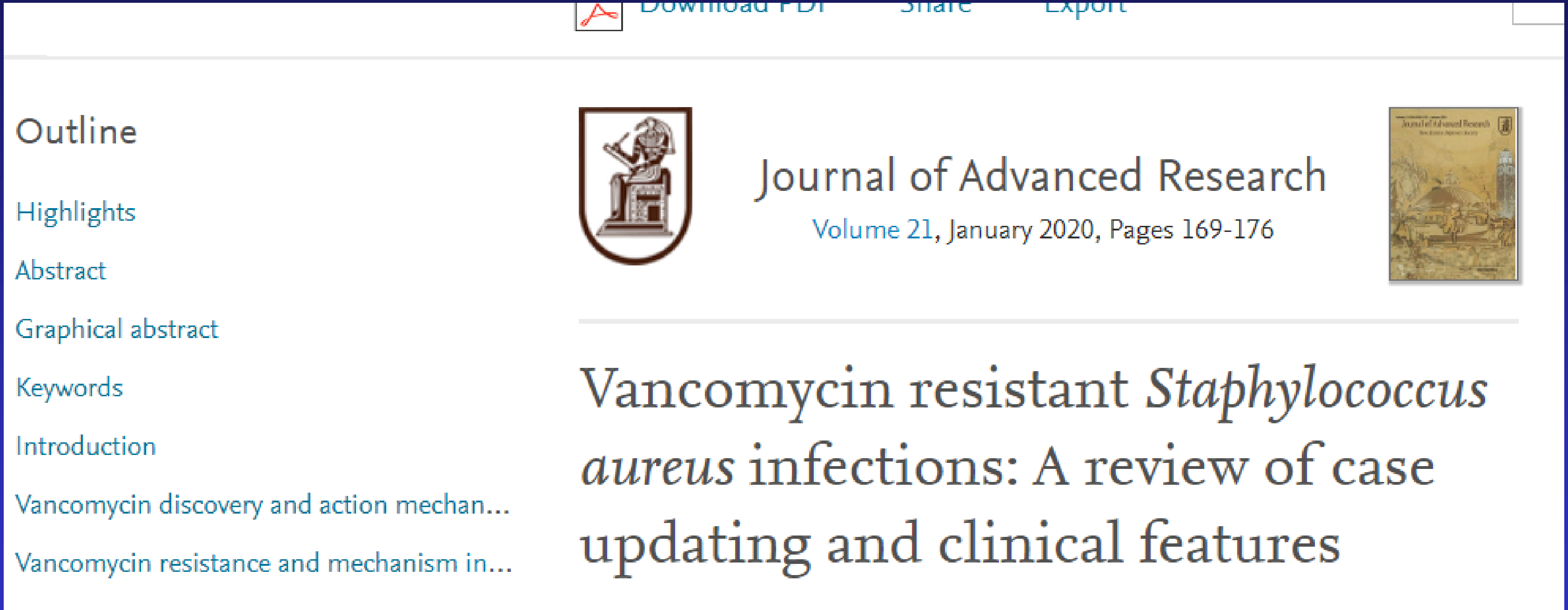
[1990s]

Vancomycin intermediate-resistant *S. aureus* (VISA)

Vancomycin-resistant Enterococci (VRE)

[2002]

Vancomycin-resistant *S. aureus* (VRSA)



Outline

Highlights

Abstract

Graphical abstract

Keywords

Introduction

Vancomycin discovery and action mechan...

Vancomycin resistance and mechanism in...

Treatment of VRSA infections

Journal of Advanced Research
Volume 21, January 2020, Pages 169-176

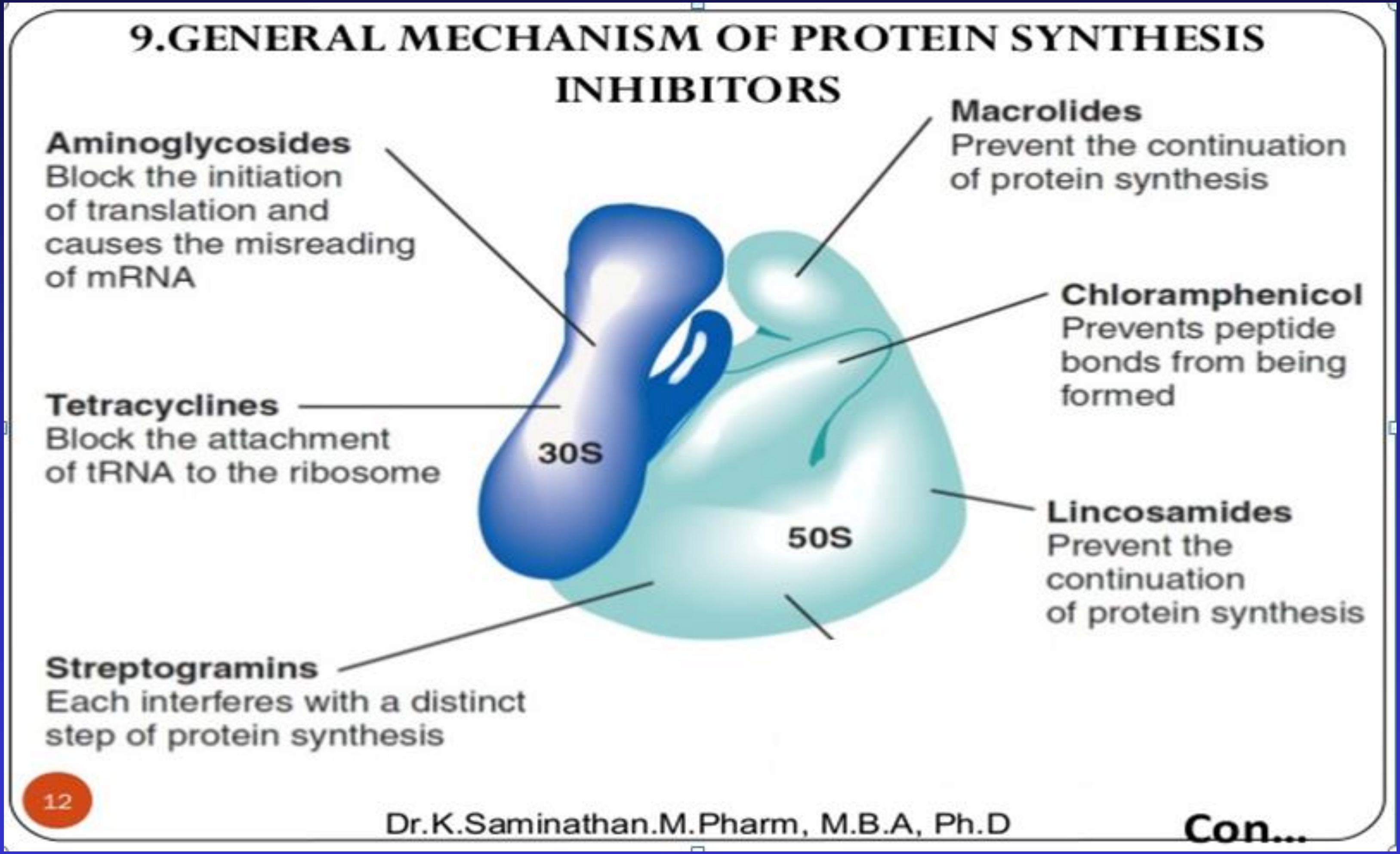
Vancomycin resistant *Staphylococcus aureus* infections: A review of case updating and clinical features

Bacitracin

- Bacitracin is a polypeptide antibiotic derived from *B. subtilis* that functions to **block cell wall formation**.
- The antibacterial spectrum of bacitracin **is gram positive** and includes staphylococci, streptococci, *Corynebacterium*, and *Clostridium*
- Bacitracin is too toxic to be used systemic treatment but is well tolerated topically. Bacitracin is commonly combined with neomycin and polymyxin B in topical antibiotic preparations.

Inhibitors of Protein Synthesis

- 70s ribosome in bacteria



9.GENERAL MECHANISM OF PROTEIN SYNTHESIS INHIBITORS

Aminoglycosides
Block the initiation of translation and causes the misreading of mRNA

Tetracyclines
Block the attachment of tRNA to the ribosome

Streptogramins
Each interferes with a distinct step of protein synthesis

Macrolides
Prevent the continuation of protein synthesis

Chloramphenicol
Prevents peptide bonds from being formed

Lincosamides
Prevent the continuation of protein synthesis

Dr.K.Saminathan.M.Pharm, M.B.A, Ph.D

Con...

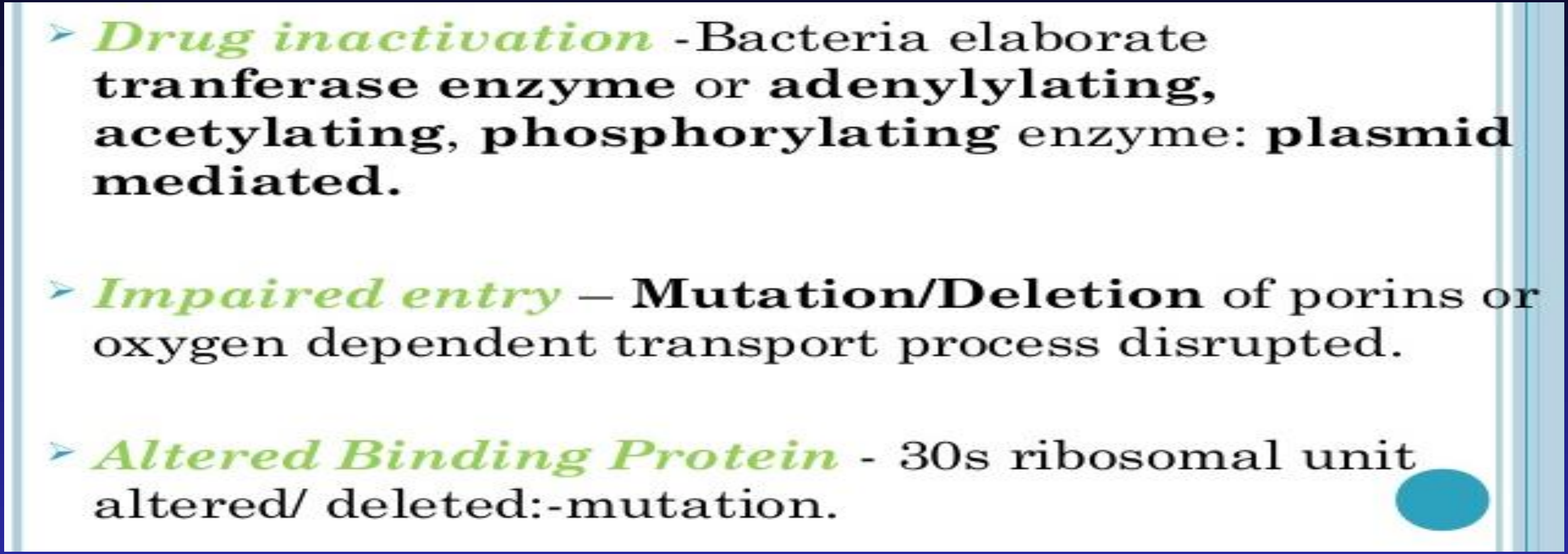
Aminoglycosides

- Streptomycin, neomycin, gentamycin, Kanamycin, tobramycin, Amikasin
- Toxicity on kidney and ear
- Mechanism:
- The aminoglycosides primarily act by binding to the aminoacyl site of 16S ribosomal RNA (16S rRNA) within the 30S ribosomal subunit, leading to **misreading** of the genetic code and **inhibition of translocation (bactericidal** inhibitors)

SPECTRUM OF ACTIVITY

- In general, aminoglycosides are active across a broad spectrum of aerobic gram-negative (Enterobacteriaceae, *Pseudomonas* spp, *Acinetobacter* spp, and *Haemophilus influenzae*.) and gram-positive organisms as well as mycobacteria (Streptomycin, tobramycin, and amikacin demonstrate favorable activity in vitro against mycobacteria).
- Of note, anaerobic bacteria are intrinsically resistant to aminoglycosides.

Resistance



- *Drug inactivation* -Bacteria elaborate **tranferase enzyme** or **adenylylating, acetylating, phosphorylating** enzyme: **plasmid mediated.**
- *Impaired entry* – **Mutation/Deletion** of porins or oxygen dependent transport process disrupted.
- *Altered Binding Protein* - 30s ribosomal unit altered/ deleted:-mutation.

- Organisms resistant to other antimicrobials (such as those producing possessing ***Klebsiella pneumoniae*** **carbapenemases [KPCs], as well as ESBLs**), are often resistant to most aminoglycosides due to the **presence of aminoglycoside-modifying enzymes.**
- **Plazomicin** (A Next-Generation Aminoglycoside) often retains activity against such isolates
- **Cross-resistance** between the specific aminoglycoside agents does occur.

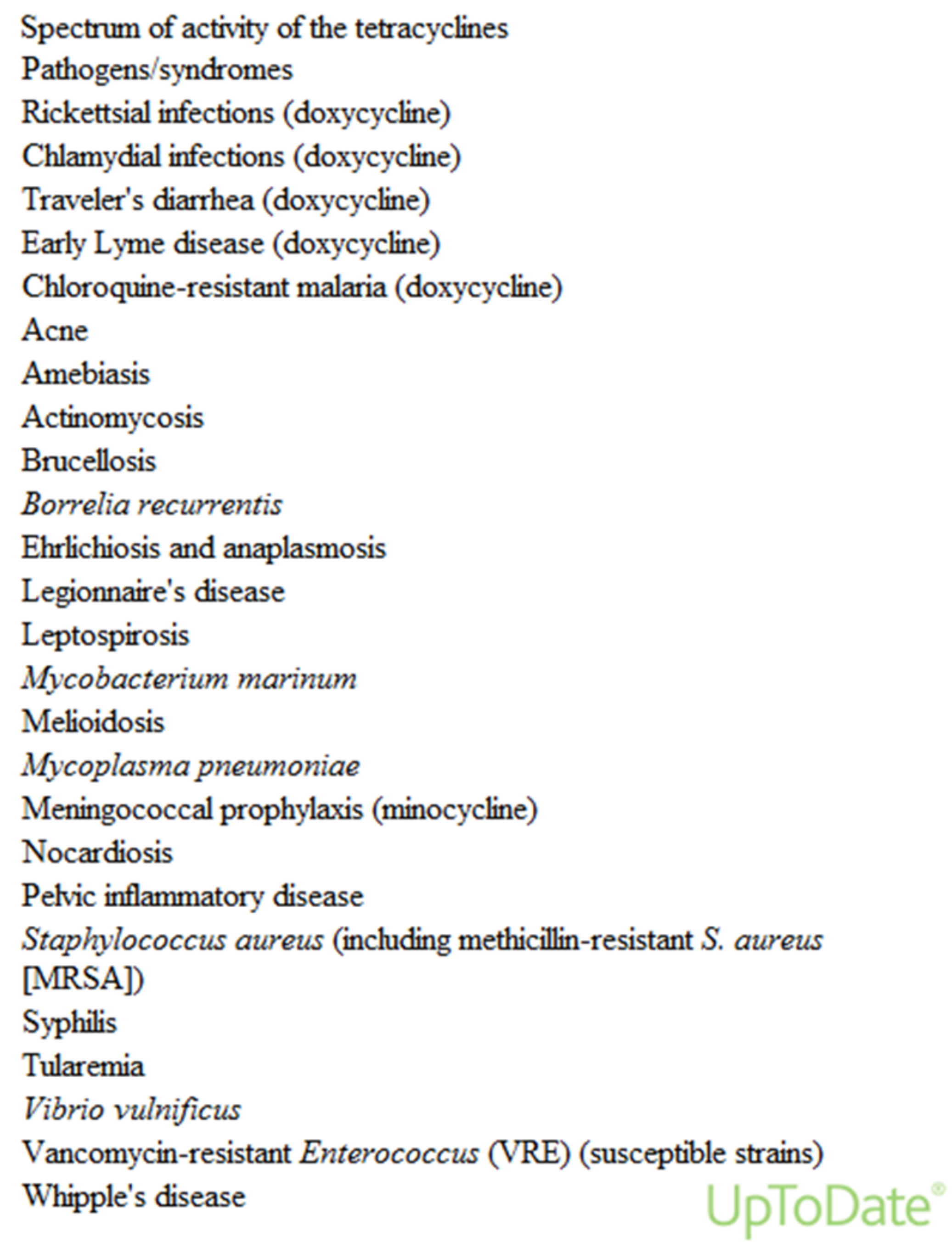
Synergism effect

- Combination of the aminoglycoside with a cell wall active agent, such as penicillin or vancomycin.
- Enterococci are **intrinsically** resistant to **moderate levels** of aminoglycosides.
- The potential for synergy in combination with a cell wall-active agent remains unless the enterococcus has **acquired** **high-level resistance** to aminoglycosides

Tetracyclines

- The first tetracycline, was discovered in 1948.
- Doxycycline and minocycline and Tigecycline.
- Newer agents approved in 2018
include eravacycline, sarecycline, and omadacycline.

- These have a broad spectrum of activity against many gram-positive, gram-negative, and anaerobic organisms (Bacteriostatic effect)



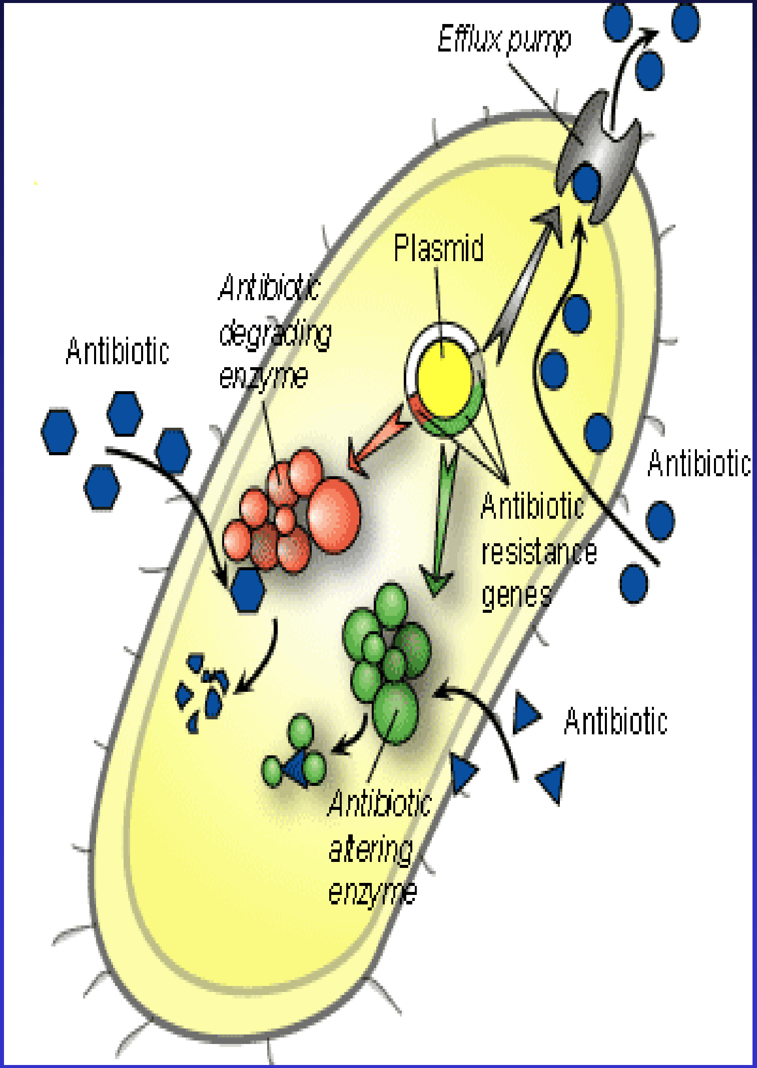
Spectrum of activity of the tetracyclines

Pathogens/syndromes
Rickettsial infections (doxycycline)
Chlamydial infections (doxycycline)
Traveler's diarrhea (doxycycline)
Early Lyme disease (doxycycline)
Chloroquine-resistant malaria (doxycycline)
Acne
Amebiasis
Actinomycosis
Brucellosis
Borrelia recurrentis
Ehrlichiosis and anaplasmosis
Legionnaire's disease
Leptospirosis
Mycobacterium marinum
Melioidosis
Mycoplasma pneumoniae
Meningococcal prophylaxis (minocycline)
Nocardiosis
Pelvic inflammatory disease
Staphylococcus aureus (including methicillin-resistant *S. aureus* [MRSA])
Syphilis
Tularemia
Vibrio vulnificus
Vancomycin-resistant *Enterococcus* (VRE) (susceptible strains)
Whipple's disease

Resistance

- Tetracyclines bind to the 30S subunit of microbial ribosomes (Blocking the attachment of aminoacyl-tRNA)

- -Efflux pump
- -Ribosomal protection (*Tet* gene products are responsible for protecting the ribosome, likely through mechanisms that induce conformational changes)


Efflux pump
Plasmid
Antibiotic degrading enzyme
Antibiotic
Antibiotic
Antibiotic resistance genes
Antibiotic
Antibiotic altering enzyme

Chloramphenicol

- Chloramphenicol binds to the 50S subunit of the ribosome by inhibits peptidyl transferase (Bacteriostatic effect).
- Resistance:
- is due to destruction of the drug by an enzyme (chloramphenicol acetyltransferase) that is under plasmid control
- Side effect :
- Bone marrow due to 70s ribosome in mitochondria and cause anemia
- Gray baby with circulatory collapse :
- Young infants have a limited capacity

  to conjugate and excrete chloramphenicol in liver

Adverse effects

Gray baby syndrome

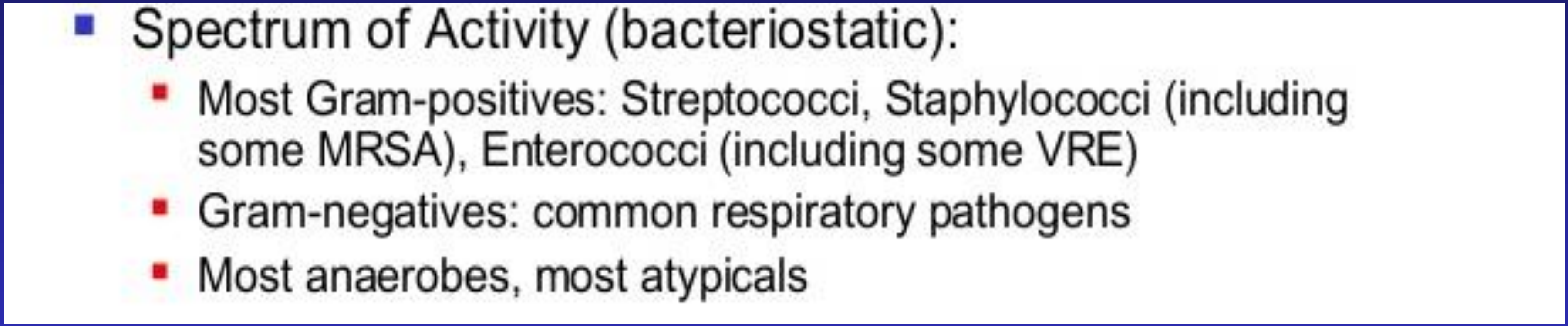
- Intravenous chloramphenicol use has been associated with the so-called gray baby syndrome.
- This phenomenon occurs in newborn infants because they do not yet have fully functional liver enzymes (i.e. UDP-glucuronyl transferase), so chloramphenicol remains unmetabolized in the body. This causes several adverse effects, including hypotension and cyanosis. The condition can be prevented by using the drug at the recommended doses, and monitoring blood levels.

Gastrointestinal disturbances:

- These conditions may occur from direct irritation and from superinfections, especially candidiasis (secondary to alteration of the intestinal microbial flora).

SPECTRUM OF ACTIVITY

- The spectrum is very broad and includes intracellular pathogens, such as chlamydiae and rickettsiae,



- Spectrum of Activity (bacteriostatic):
  - Most Gram-positives: Streptococci, Staphylococci (including some MRSA), Enterococci (including some VRE)
  - Gram-negatives: common respiratory pathogens
  - Most anaerobes, most atypicals

- P. aeruginosa and M. tuberculosis are usually resistant

Clindamycin and Lincomycin

- MECHANISM OF ACTION — Both works primarily by binding to the 50s ribosomal subunit of bacteria.
- This agent disrupts protein synthesis by interfering with the transpeptidation reaction, which thereby **inhibits early chain elongation(bacteriostatic** effect).

SPECTRUM OF ACTIVITY

- Clindamycin generally has in vitro activity against staphylococci, viridans group streptococci, *Streptococcus pyogenes*, and *Streptococcus pneumoniae*.
- It also demonstrates potent activity against anaerobes such as *B. fragilis*, *Clostridium perfringens*, *Fusobacterium* spp, *Prevotella melaninogenicus*, and *Peptostreptococcus* spp

RESISTANCE

- There are several mechanisms of bacterial resistance to clindamycin, including modification of the target, inactivation of the drug, or efflux of the drug.
- Cross-resistance of *S. aureus* to lincomycin and clindamycin is complete.
- In addition, bacteria that are erythromycin-resistant may quickly develop resistance when exposed to clindamycin.
- *C. difficile* is often resistant to clindamycin but susceptible to metronidazole and vancomycin. Pseudomembranous colitis caused by overgrowth of *C. difficile* has been reported in 0.1 to 10 percent of patients receiving clindamycin and can be severe or life threatening.

Macrolides and **Azalides**

- **Erythromycin, roxithromycin, azithromycin and clarithromycin**
- **Bacteriostatic activity** or inhibits growth of bacteria by binding to the 50s subunit of the bacterial rRNA complex.
-

SPECTRUM OF ACTIVITY

- Azithromycin and clarithromycin have a **broader spectrum of activity than** erythromycin and are therefore used in a variety of infections including infections of the respiratory tract, mycobacterial infections, and STDs.

- *S. pneumoniae, Haemophilus spp, Moraxella catarrhalis*, and atypical pneumonia pathogens, including *L. pneumophila, Chlamydia pneumoniae, and Mycoplasma pneumoniae*.

RESISTANCE

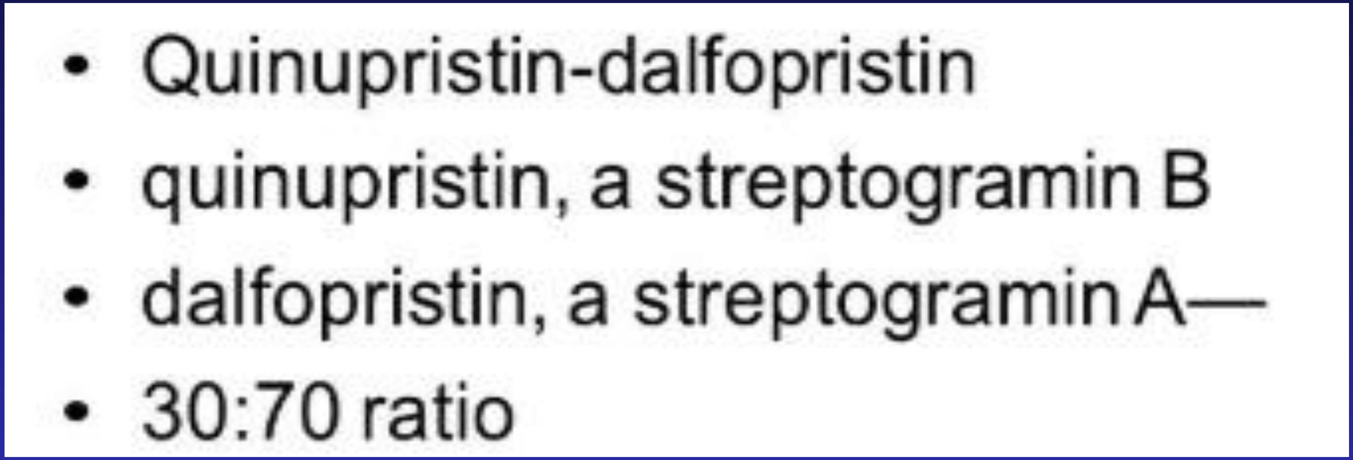
- Mechanisms of resistance to azithromycin or clarithromycin are the same as or similar to those of erythromycin.
- Two main mechanisms of acquired macrolide resistance have been described:
- ●Methylases encoded by the *erm* (erythromycin ribosome methylase) genes (*ermA*, *ermB*, *ermC*) alter the macrolide-binding site on the bacterial ribosomal RNA, usually conferring a **high degree** of macrolide resistance

- Active macrolide **efflux pumps**, encoded by the *mef* (macrolide efflux) *msrA* and *msrB* genes, confer a low to moderate degree of macrolide resistance.
- Cross-resistance among erythromycin, azithromycin, and clarithromycin in gram-positive organisms

MUPIROCIN

- The useful activity is **restricted (narrow spectrum)** to gram-positive cocci, in which it presumably halts protein synthesis by **binding to isoleucyl tRNA synthetase** as it does in E. coli.
- it is used only for topical application in skin infections and to eradicate staphylococci from nasal carriers

Streptogramins



- Quinupristin-dalfopristin
- quinupristin, a streptogramin B
- dalfopristin, a streptogramin A—
- 30:70 ratio

- Quinupristin binds to the bacterial 50S ribosomal subunit, thereby inhibiting peptide chain elongation.
- Quinupristin is primarily effective against gram-positive cocci.
- No activity against Enterobacteriaceae and Pseudomonas.

Nucleic Acid Synthesis Inhibitors
Rifamycins and Quinolones

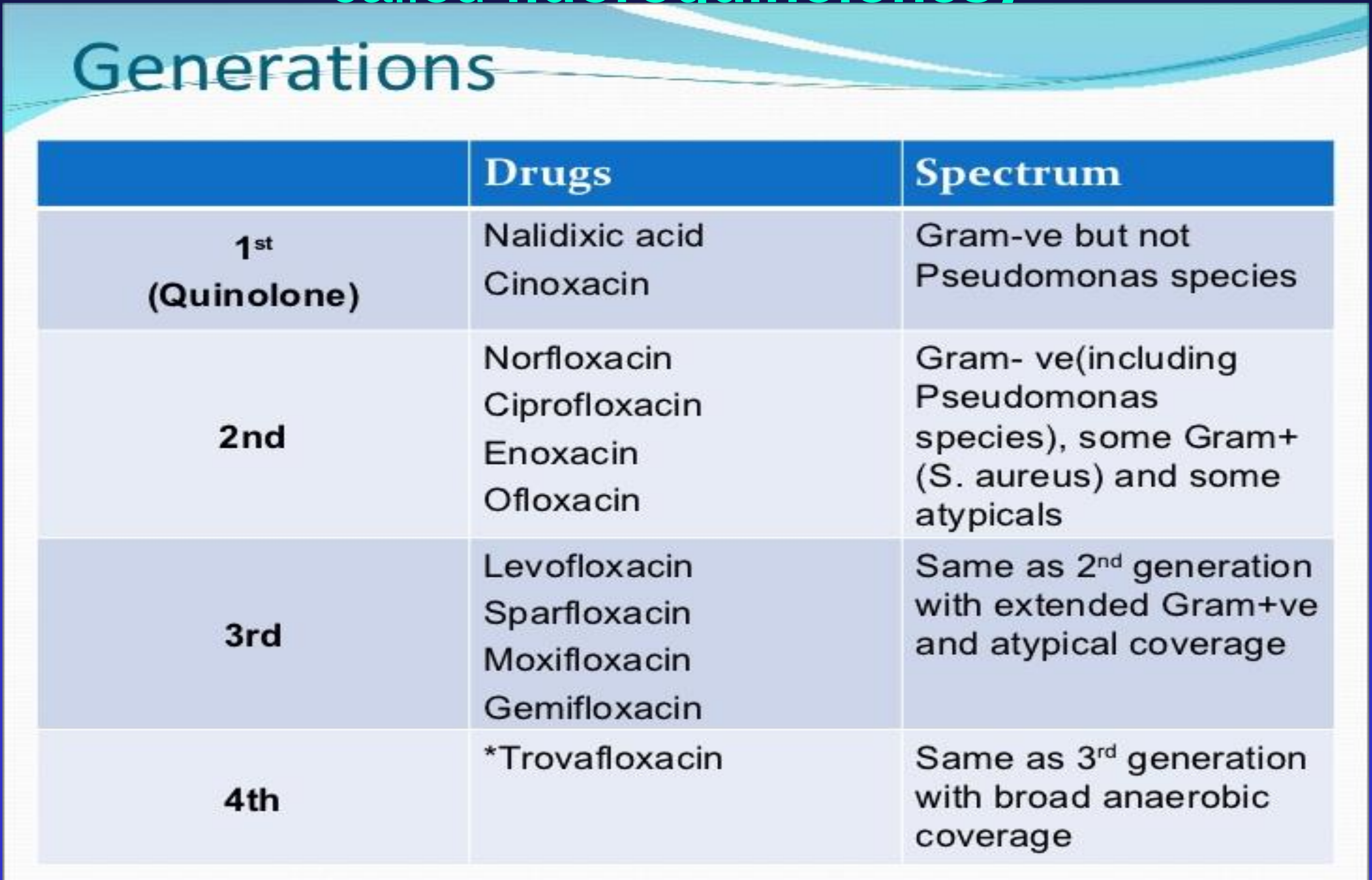
- **Rifamycins**: rifampin, rifapentine, and rifabutin: inhibits RNA synthesis (RNA polymerase).
- Of these, rifampin is most commonly used, either as first-line therapy (in combination with other agents) for treatment of mycobacterial disease (including tuberculosis) or for select invasive staphylococcal infections
- Rifabutin active in the prevention of infection due to *M avium* complex. Also is effect on G+ and G- cocci

Resistance

- Resistance to rifampin arises due to missense mutations in the ***rpoB*** **gene** and occurs in a variety of bacteria including *Mycobacterium tuberculosis*, *Staphylococcus aureus* (including MRSA), *Streptococcus pneumoniae*, and Rickettsiae

- The rate of **spontaneous resistance** of *M. tuberculosis* via single-step mutation to rifampin is 1 in 10^8 bacilli.
- The rate of resistance in other types of bacteria (eg, *Escherichia coli*, *S. aureus*, *Streptococcus* spp, and *N. meningitidis*) is much higher.
- Since the rate of development of resistance is both high and predictable, rifampin should be used as **monotherapy only** for prophylaxis against *N. meningitidis* or *H. influenzae*, or for *M. tuberculosis* where the organism burden is relatively low

Qinolones and Fluoroquinolones (**Quinolones** with a fluorine atom are called **fluoroquinolones**)



Generations

	Drugs	Spectrum
1st (Quinolone)	Nalidixic acid Cinoxacin	Gram-ve but not Pseudomonas species
2nd	Norfloxacin Ciprofloxacin Enoxacin Ofloxacin	Gram- ve(including Pseudomonas species), some Gram+ (S. aureus) and some atypicals
3rd	Levofloxacin Sparfloxacin Moxifloxacin Gemifloxacin	Same as 2nd generation with extended Gram+ve and atypical coverage
4th	*Trovafloxacin	Same as 3rd generation with broad anaerobic coverage

- NA is effective for urinary tract infections because it is concentrated in the urine, but it has little systemic activity.
- Fluorination of the quinolone structure was subsequently found to produce compounds that were up to **60 times more active** than nalidixic acid and killed a wider range of organisms.
- Overall, quinolones are extremely active against Gram-negative organisms and most have useful activity against *P.aeruginosa*, mycobacteria and *L.pneumophila*.
-
- Most are less active against Gram-positive organisms (resistance commonly emerges) and anaerobes.

- Mechanism:
- blocking of the DNA gyrase A.

Chromosomal resistance:

an alteration in the A subunit of the target enzyme, DNA gyrase;

or a change in outer membrane permeability

Trimethoprim-sulfamethoxazole (TMP-SMX)

- Also known as co-trimoxazole, is a combination of two antimicrobial agents that act synergistically against a wide variety of bacteria.

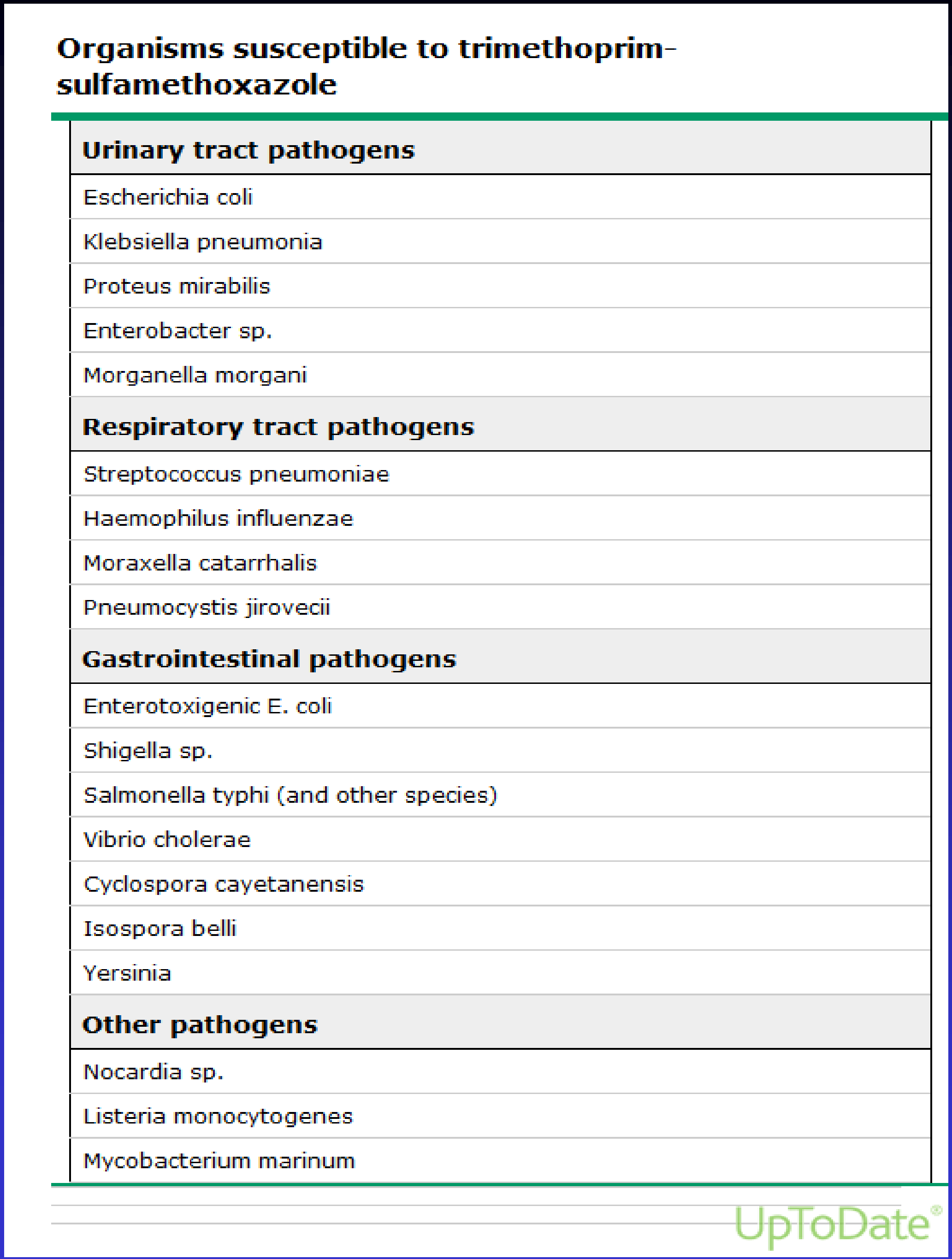
MECHANISM OF ACTION

- The two components, work sequentially to inhibit enzyme systems involved in the bacterial synthesis of tetrahydrofolic acid (THF).
- SMX is a structural analog of para-aminobenzoic acid (PABA) and competes with PABA to inhibit the synthesis of dihydrofolic acid.
- TMP binds to bacterial dihydrofolate reductase.
- Result:

Reduced availability of THF inhibits thymidine synthesis and subsequently DNA synthesis

SPECTRUM OF ACTIVITY

- TMP-SMX is effective against a wide variety of aerobic gram-positive and gram-negative bacteria, and some protozoa



Organisms susceptible to trimethoprim-sulfamethoxazole

Urinary tract pathogens
Escherichia coli
Klebsiella pneumonia
Proteus mirabilis
Enterobacter sp.
Morganella morgani
Respiratory tract pathogens
Streptococcus pneumoniae
Haemophilus influenzae
Moraxella catarrhalis
Pneumocystis jirovecii
Gastrointestinal pathogens
Enterotoxigenic E. coli
Shigella sp.
Salmonella typhi (and other species)
Vibrio cholerae
Cyclospora cayetanensis
Isospora belli
Yersinia
Other pathogens
Nocardia sp.
Listeria monocytogenes
Mycobacterium marinum

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RESISTANCE

- Some bacteria have a decreased permeability for TMP-SMX,
- Have a target enzyme with decreased affinity for the drugs.
- Some bacteria (eg, *Pseudomonas aeruginosa*) have an active efflux mechanism to eliminate the drug from the cell
- Naturally resistant bacteria to SMX (eg, *E. faecalis*) are typically auxotrophic for folic acid.

Cell membrane

- Polymyxins comprise
- polymyxin B and polymyxin E (also known as colistin) are in clinical use.

- Polymyxins are bactericidal drugs that bind to lipopolysaccharides (LPS) and phospholipids in the outer cell membrane of gram-negative bacteria

- Polymyxins have a **narrow** antibacterial spectrum limited to a subset of gram-negative bacilli.
- They are primarily used for infections due to multidrug-resistant organisms, such as carbapenem-resistant Enterobacteriaceae (Escherichia coli, Klebsiella pneumoniae, some Enterobacter spp), Pseudomonas aeruginosa, and Acinetobacter baumannii.
- Other susceptible organisms include Haemophilus influenzae, Bordetella pertussis, Legionella pneumophila, Salmonella spp, Shigella spp, and the majority of Stenotrophomonas maltophilia strains

Other antibiotics

- Dapsone, metronidazole, isoniazid, ethambutol, cycloserine.

Antibiotic prophylaxis

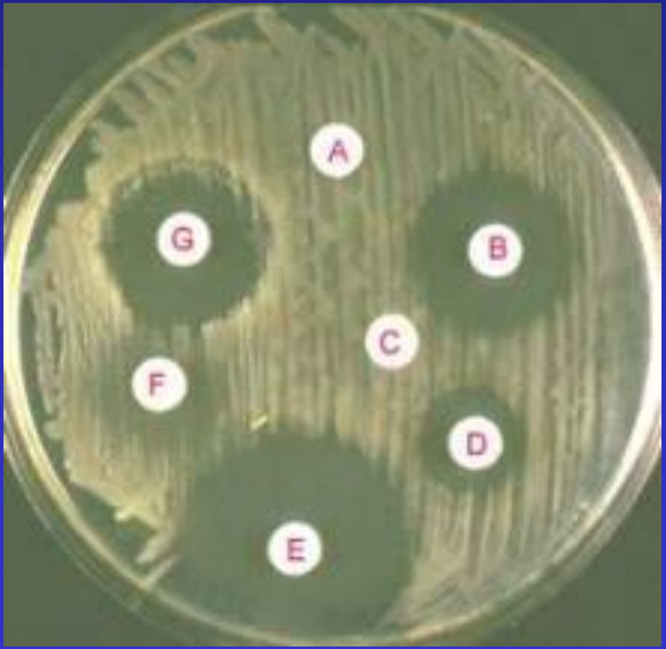
- It is the use of **antibiotics** before surgery or a dental procedure to prevent a bacterial infection.

- خطرات ناشی از استفاده از آنتی بیوتیک بدون تشخیص بیماری؟

Antimicrobial susceptibility testing (AST)- Disk Diffusion

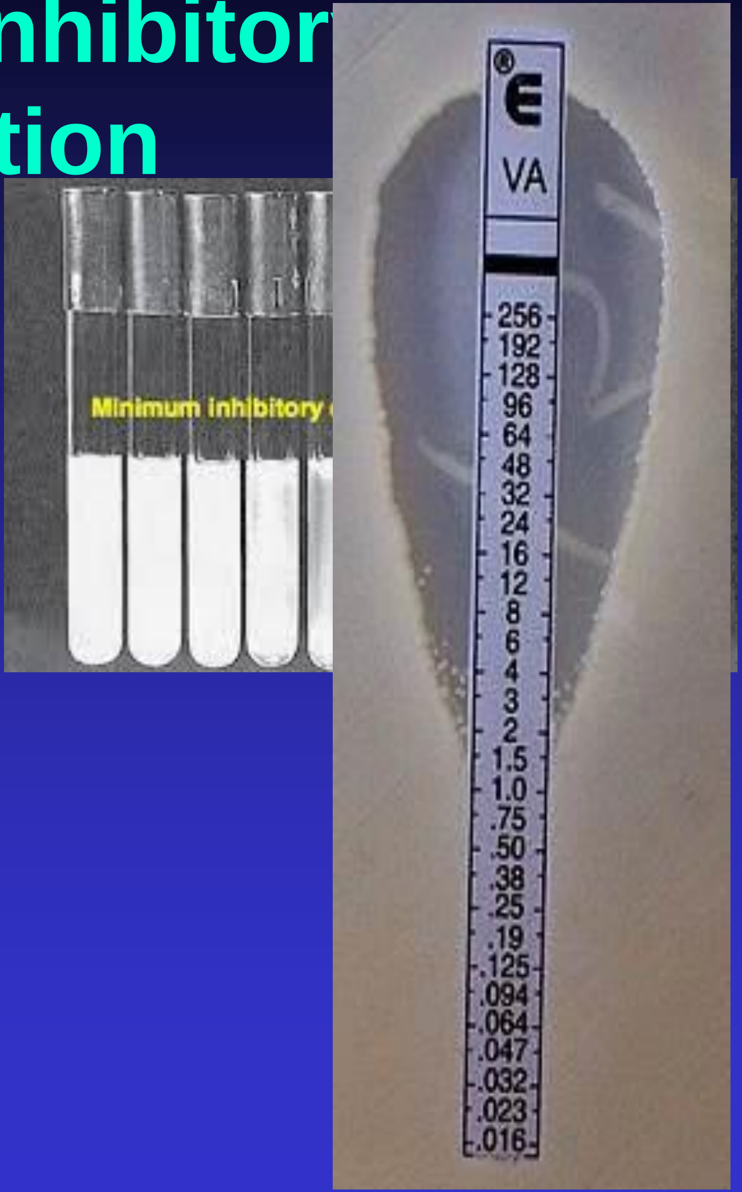
- The disc diffusion method was described by Bauer and Kirby in the 1**950s/1960s**. After more than 70 years, disc diffusion is still a widely used procedure for antimicrobial susceptibility testing (AST) in the clinical microbiological laboratory.

- Traditionally, the basis of clinical AST reporting is categorization into susceptible (S), intermediate (I), and resistant (R)—referring to the likelihood of clinical success



Antimicrobial susceptibility testing

MIC: Minimum **inhibitor** **concentration**



- The minimum inhibitory concentration (MIC) is defined as the last tube in the dilution series which exhibited no growth.

- Broth Dilution
- Epsilometer test (**E-test**) method.

MBC: Minimum bactericidal concentration

The MBC is measured by subculturing the broths used for MIC determination onto fresh agar plates.

MBC is the lowest concentration of a drug that results in killing 99.9% of the bacteria being tested.

For example

The MIC or the lowest concentration inhibiting visible growth of bacteria is found to be **6 µg/ml** in case of doxycycline in a study.
MBC is found to be **8 µg/ml** for doxycycline for bacterial culture.

This suggests that
a higher concentration of drug is required to kill bacteria completely.

Clinical and Laboratory Standards Institute®

28th Edition

M100

Performance Standards for Antimicrobial Susceptibility Testing

EUCAST
EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING

European Society of Clinical Microbiology and Infectious Diseases

Susceptible

The susceptible category is defined as likely therapeutic success for the **individual species/drug combination** tested if recommended standard dosing is applied

Intermediate

The intermediate category is defined as uncertain therapeutic success for the individual species/drug combination tested by EUCAST.

EUCAST intended for compounds for which dosing can be increased.

CLSI defines the intermediate category as a lower response rate than for susceptible isolates, but clinical efficacy if the drug accumulates at the site of infection.

Intermediate

- The intermediate category helps to prevent serious categorization errors resulting from imprecision of inhibition zone readings

Resistant

- The resistant category implies a high likelihood of therapeutic failure (EUCAST) or no reliable clinical efficacy (CLSI).

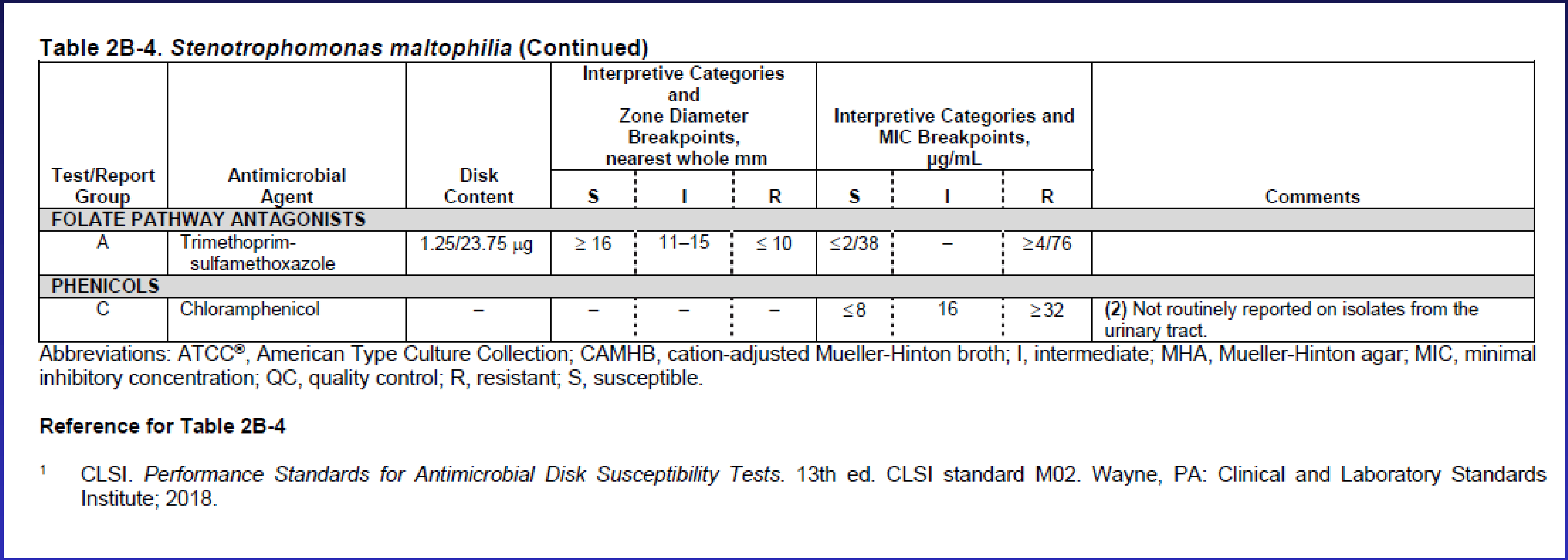


Table 2B-4. *Stenotrophomonas maltophilia* (Continued)

Test/Report Group	Antimicrobial Agent	Disk Content	Interpretive Categories and Zone Diameter Breakpoints, nearest whole mm			Interpretive Categories and MIC Breakpoints, µg/mL			Comments
			S	I	R	S	I	R	
FOLATE PATHWAY ANTAGONISTS									
A	Trimethoprim-sulfamethoxazole	1.25/23.75 µg	≥ 16	11–15	≤ 10	≤2/38	–	≥4/76	
PHENICOLS									
C	Chloramphenicol	–	–	–	–	≤8	16	≥32	**(2)** Not routinely reported on isolates from the urinary tract.

Abbreviations: ATCC®, American Type Culture Collection; CAMHB, cation-adjusted Mueller-Hinton broth; I, intermediate; MHA, Mueller-Hinton agar; MIC, minimal inhibitory concentration; QC, quality control; R, resistant; S, susceptible.

Reference for Table 2B-4

[1] CLSI. *Performance Standards for Antimicrobial Disk Susceptibility Tests*. 13th ed. CLSI standard M02. Wayne, PA: Clinical and Laboratory Standards Institute; 2018.

1. **“Pandrug Resistant (PDR):**

To all classes of antibiotics

(in the Greek language the prefix “pan-” means “all” or “whole”)

1. **Extensive Drug Resistant:**

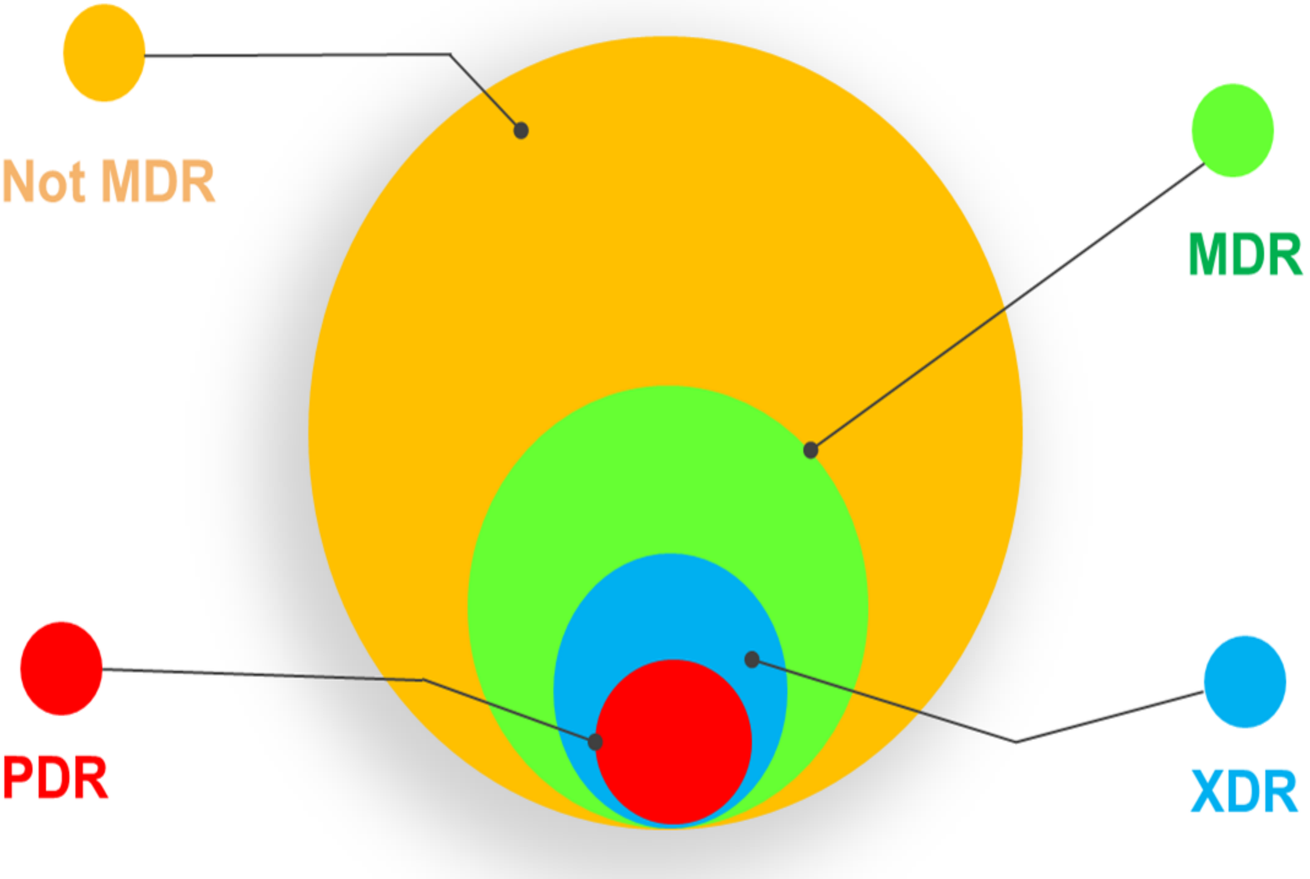
To all classes of antibiotics except 1 or 2 (colistin-tygecycline)

2. **Multidrug Resistant:**

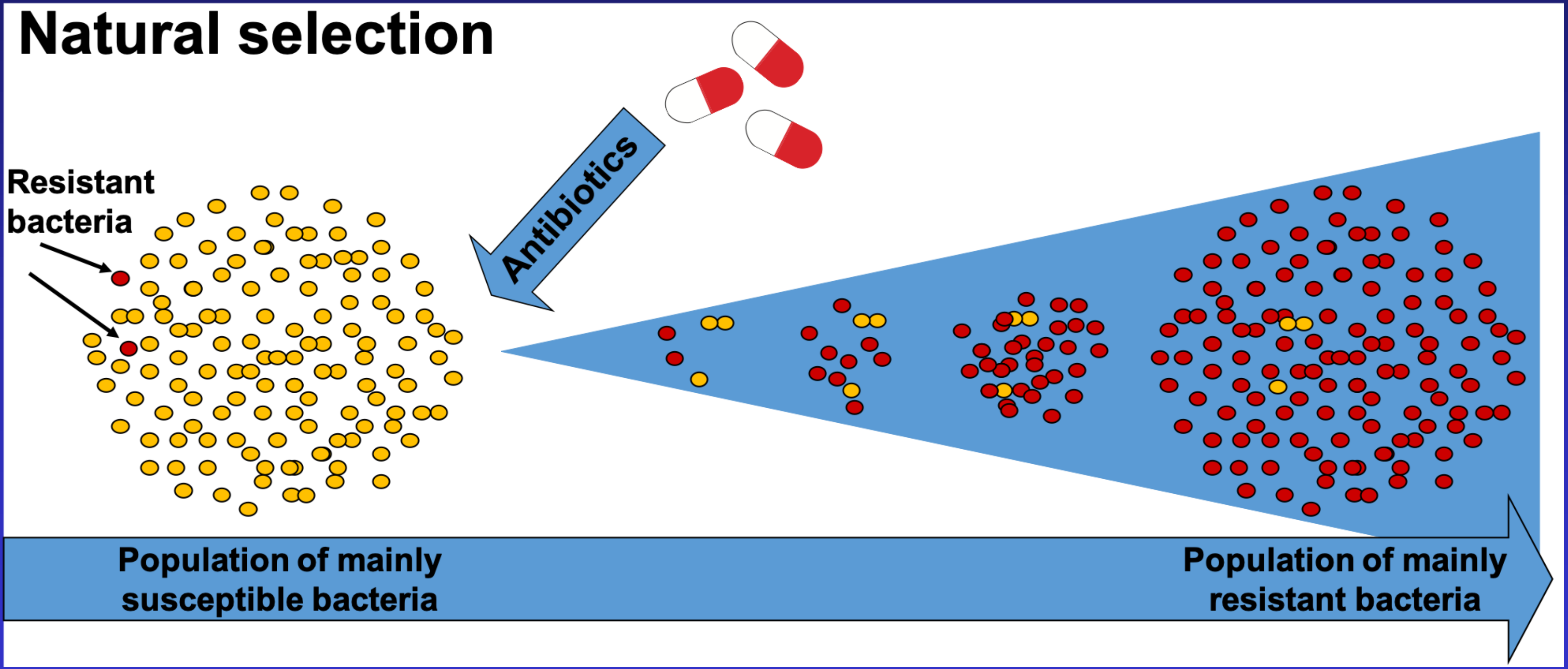
Resistance to ≥3 major classes of antibiotics

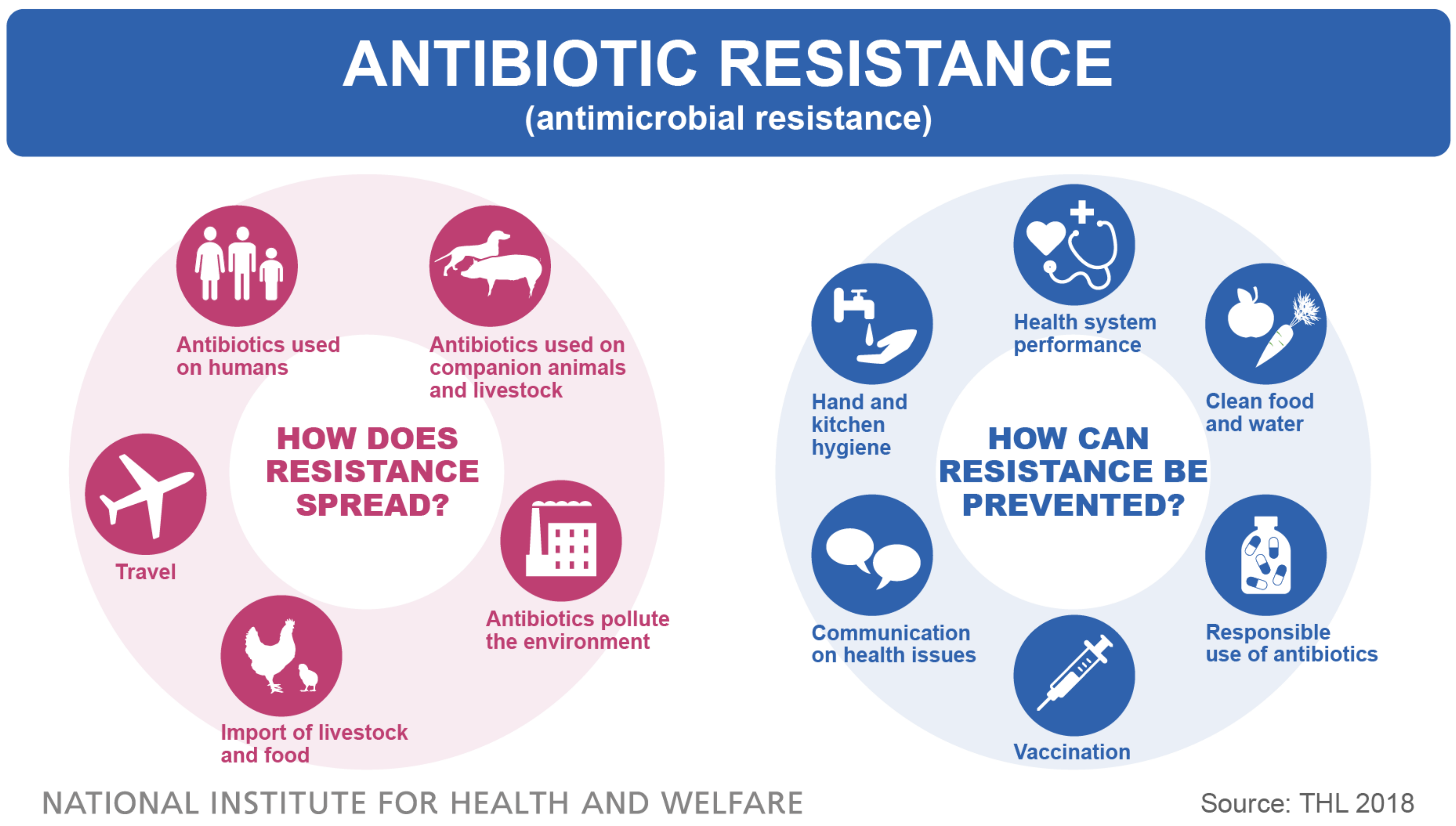
Falagas ME, Karageorgopoulos DE. CID 2008;46:1121

Diagram showing the relationship of MDR, XDR and PDR to each other



Antibiotic Selection for Resistant Bacteria


Natural selection
Resistant bacteria
Antibiotics
Population of mainly susceptible bacteria
Population of mainly resistant bacteria



ANTIBIOTIC RESISTANCE

(antimicrobial resistance)

HOW DOES RESISTANCE SPREAD?

- Antibiotics used on humans
- Antibiotics used on companion animals and livestock
- Antibiotics pollute the environment
- Import of livestock and food
- Travel

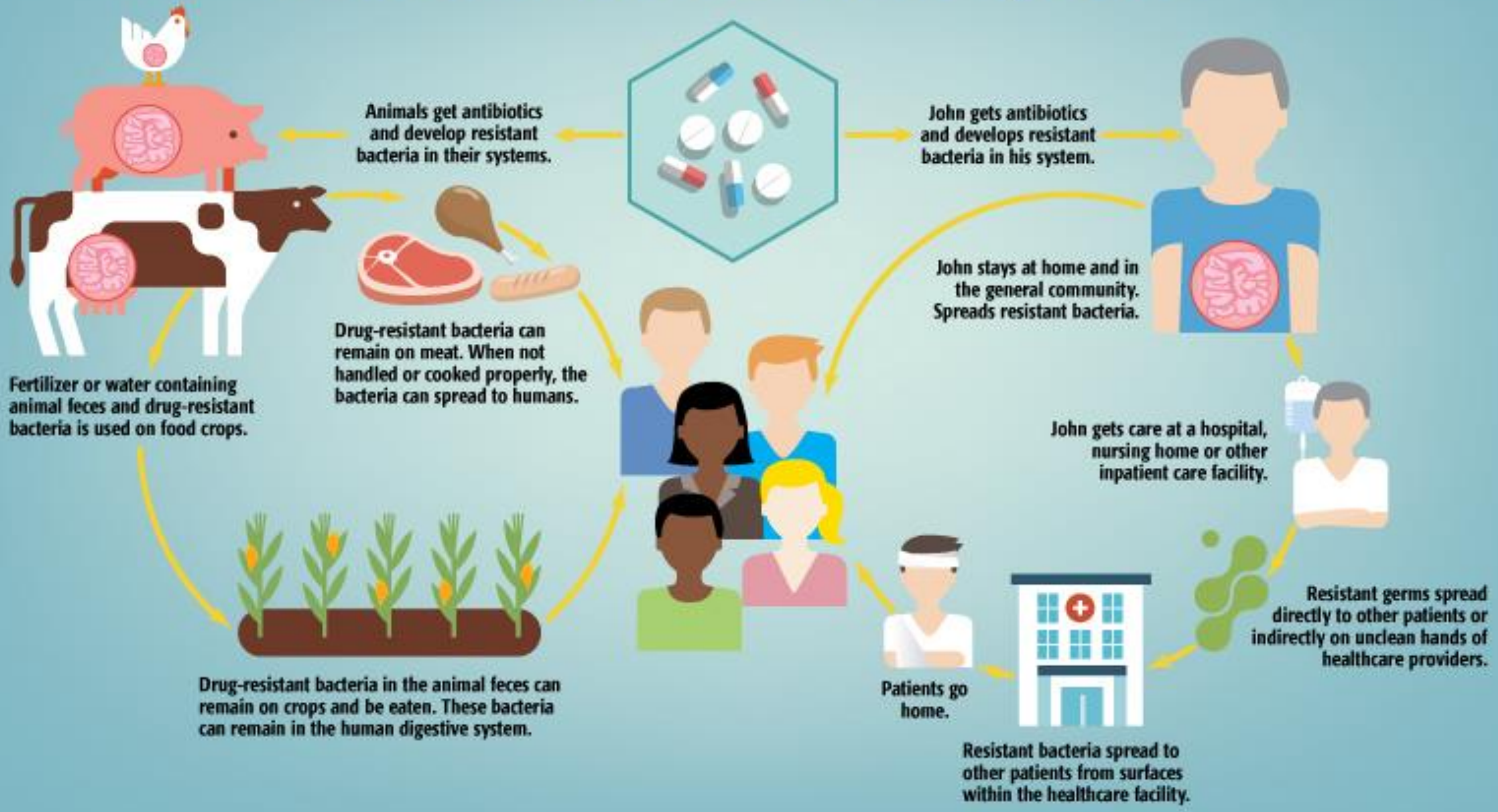
HOW CAN RESISTANCE BE PREVENTED?

- Health system performance
- Clean food and water
- Responsible use of antibiotics
- Vaccination
- Communication on health issues
- Hand and kitchen hygiene

NATIONAL INSTITUTE FOR HEALTH AND WELFARE

Source: THL 2018

How Antibiotic Resistance Spreads



Animals get antibiotics and develop resistant bacteria in their systems.

Drug-resistant bacteria can remain on meat. When not handled or cooked properly, the bacteria can spread to humans.

Fertilizer or water containing animal feces and drug-resistant bacteria is used on food crops.

Drug-resistant bacteria in the animal feces can remain on crops and be eaten. These bacteria can remain in the human digestive system.

John gets antibiotics and develops resistant bacteria in his system.

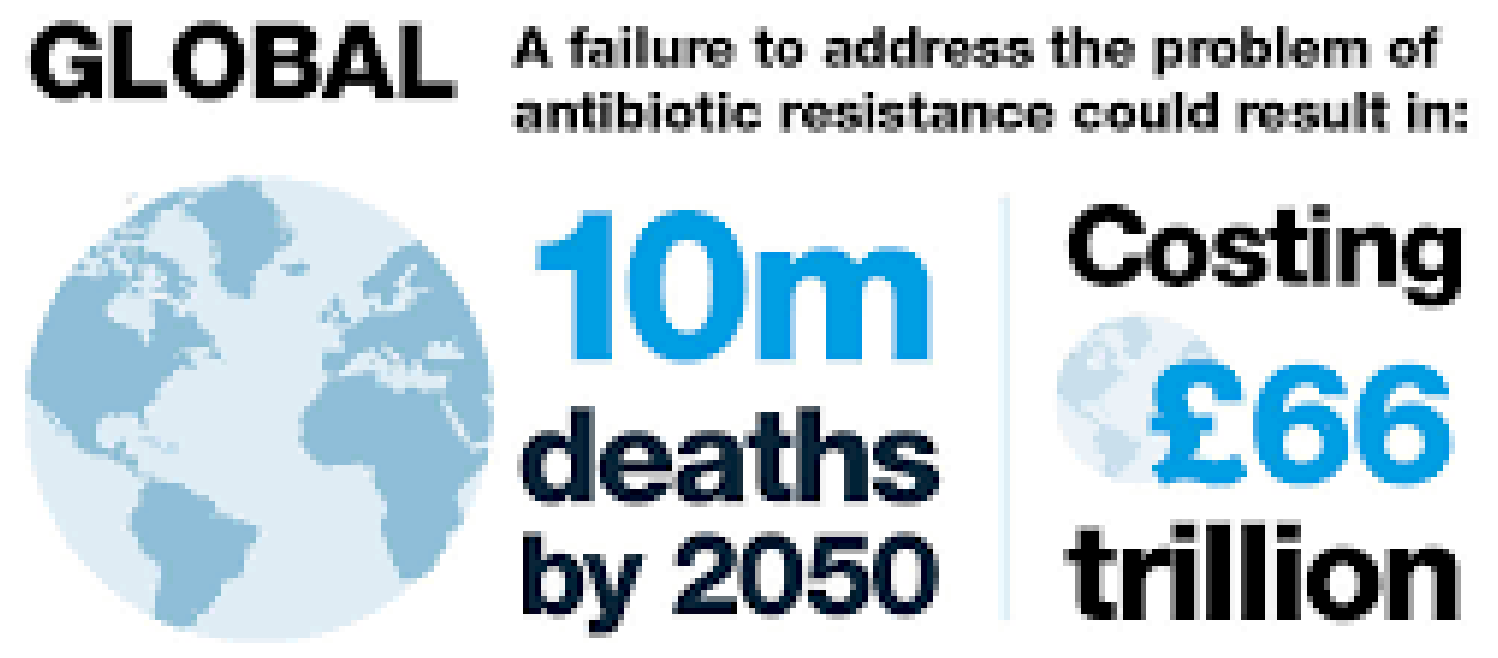
John stays at home and in the general community. Spreads resistant bacteria.

John gets care at a hospital, nursing home or other inpatient care facility.

Resistant germs spread directly to other patients or indirectly on unclean hands of healthcare providers.

Resistant bacteria spread to other patients from surfaces within the healthcare facility.

Patients go home.



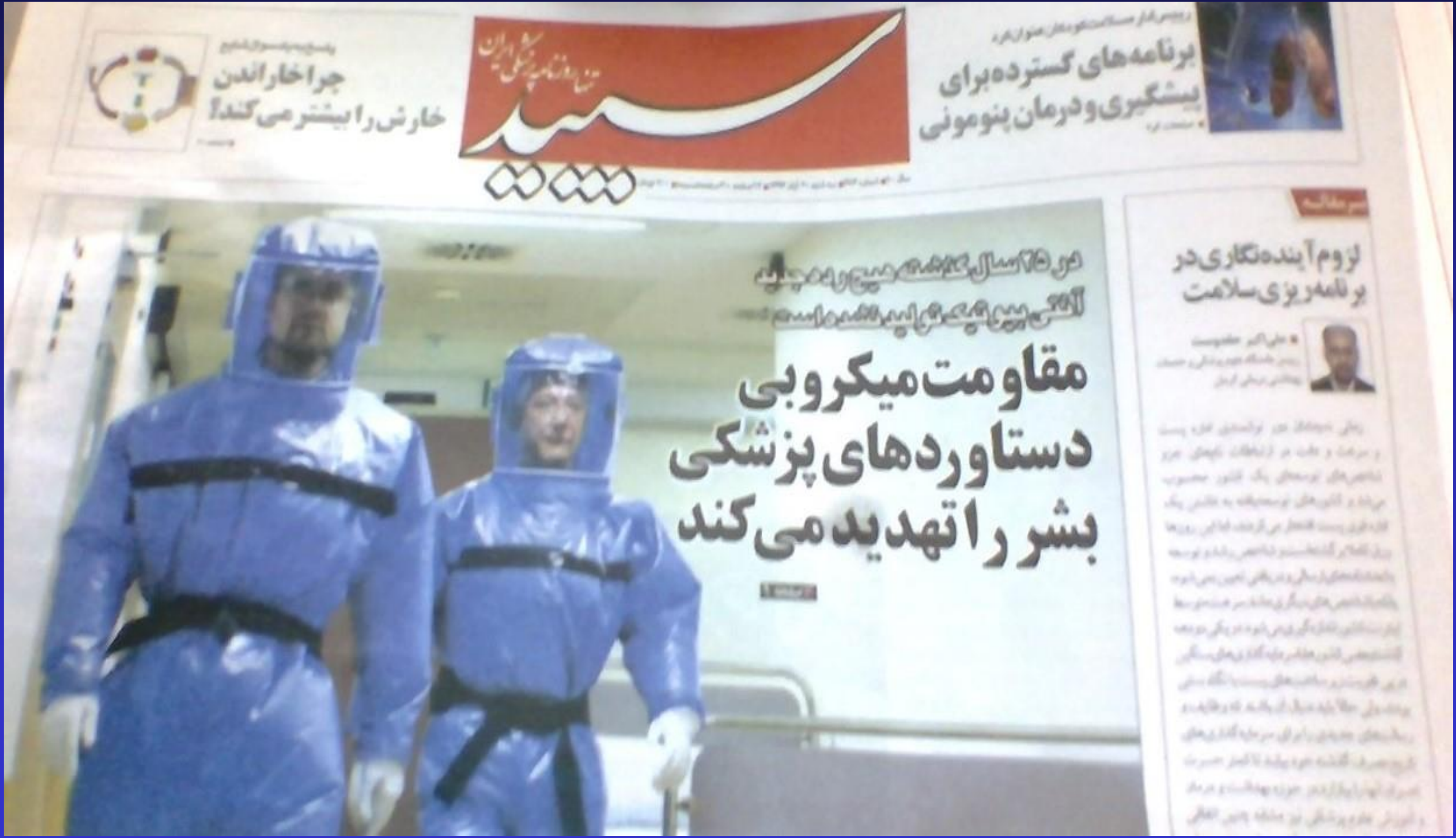
GLOBAL

A failure to address the problem of antibiotic resistance could result in:

10m deaths by 2050

Costing £66 trillion

Resistance mechansims



سپید

تنها روزنامه پزشکی ایران

چرا خاراندن خارش را بیشتر می‌کند!

برنامه‌های گسترده برای پیشگیری و درمان پنومونی

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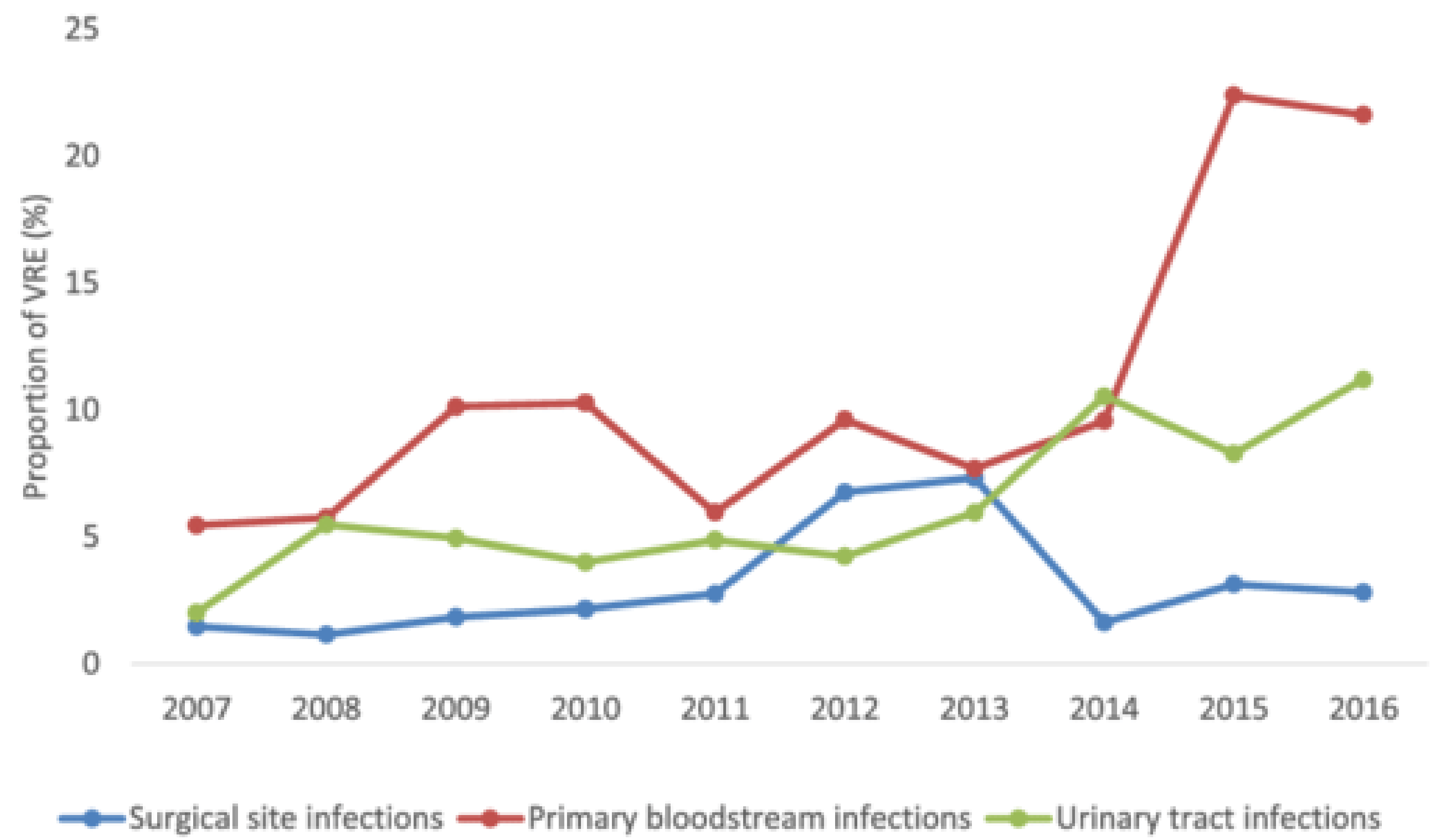
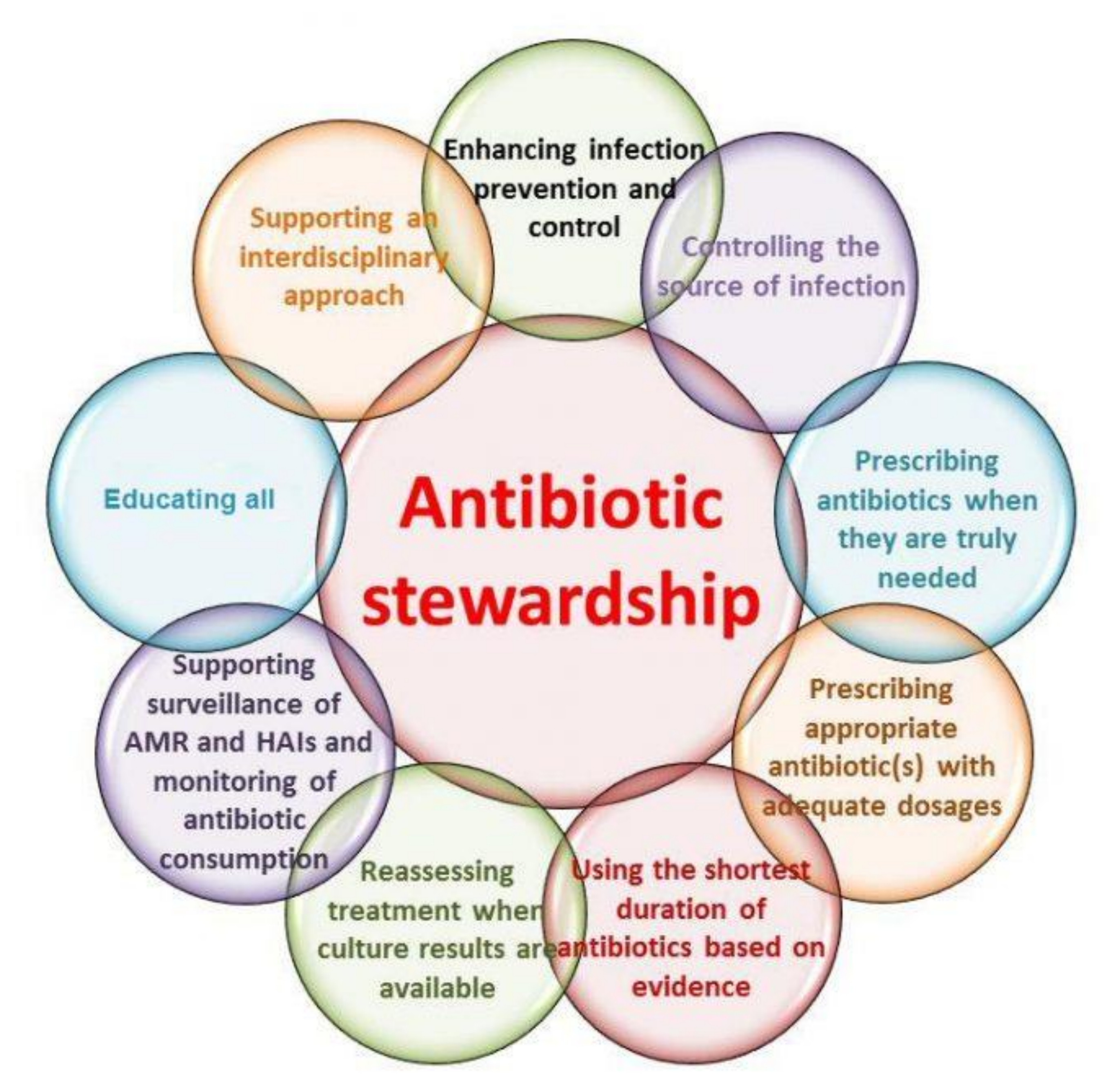
مقاومت میکروبی دستاوردهای پزشکی بشر را تهدید می‌کند

سرمقاله

لزوم آینده‌نگاری در برنامه‌ریزی سلامت

Vancomycin Resistant Enterococci





Antibiotic stewardship

Enhancing infection prevention and control

Controlling the source of infection

Prescribing antibiotics when they are truly needed

Prescribing appropriate antibiotic(s) with adequate dosages

Using the shortest duration of antibiotics based on evidence

Reassessing treatment when culture results are available

Supporting surveillance of AMR and HAIs and monitoring of antibiotic consumption

Educating all

Supporting an interdisciplinary approach

Shams *et al. BMC Res Notes* (2018) 11:314
https://doi.org/10.1186/s13104-018-3406-6

BMC Research Notes

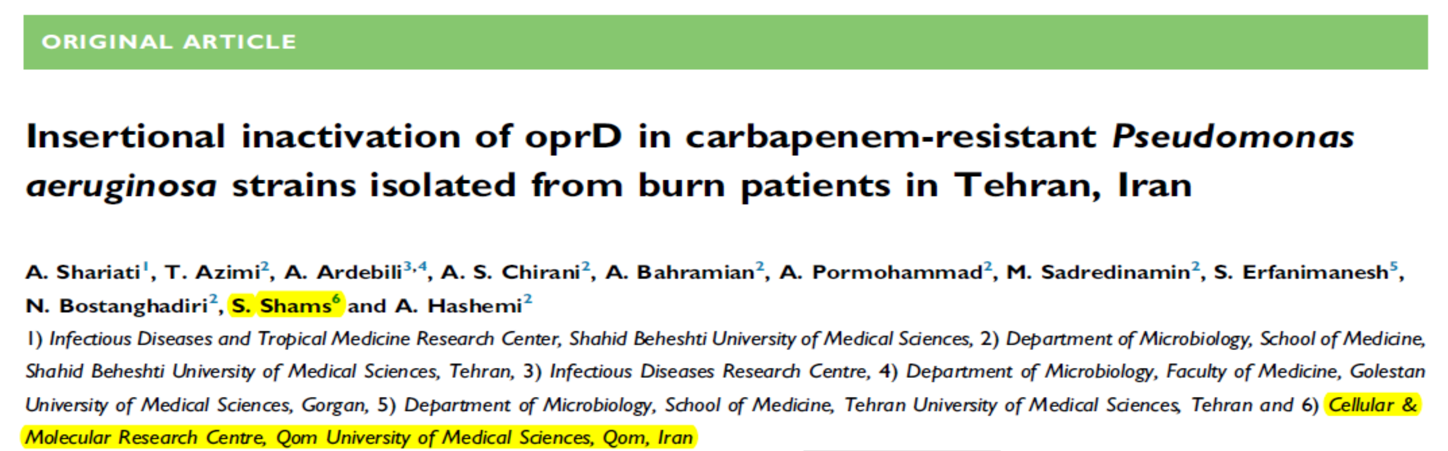
RESEARCH NOTE **Open Access**

Imipenem resistance in clinical *Escherichia coli* from Qom, Iran

Saeed Shams[1*], Ali Hashemi[2], Mohammad Esmkhani[3], Somaye Kermani[1], Elham Shams[1]
and Alessandra Piccirillo[4]

Abstract

Ob



ORIGINAL ARTICLE

Insertional inactivation of oprD in carbapenem-resistant *Pseudomonas aeruginosa* strains isolated from burn patients in Tehran, Iran

A. Shariati[1], T. Azimi[2], A. Ardebili[3,4], A. S. Chirani[2], A. Bahramian[2], A. Pormohammad[2], M. Sadredinamin[2], S. Erfanimanesh[5], N. Bostanghadiri[2], S. Shams[6] and A. Hashemi[2]

1) Infectious Diseases and Tropical Medicine Research Center, Shahid Beheshti University of Medical Sciences, 2) Department of Microbiology, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, 3) Infectious Diseases Research Centre, 4) Department of Microbiology, Faculty of Medicine, Golestan University of Medical Sciences, Gorgan, 5) Department of Microbiology, School of Medicine, Tehran University of Medical Sciences, Tehran and 6) Cellular & Molecular Research Centre, Qom University of Medical Sciences, Qom, Iran

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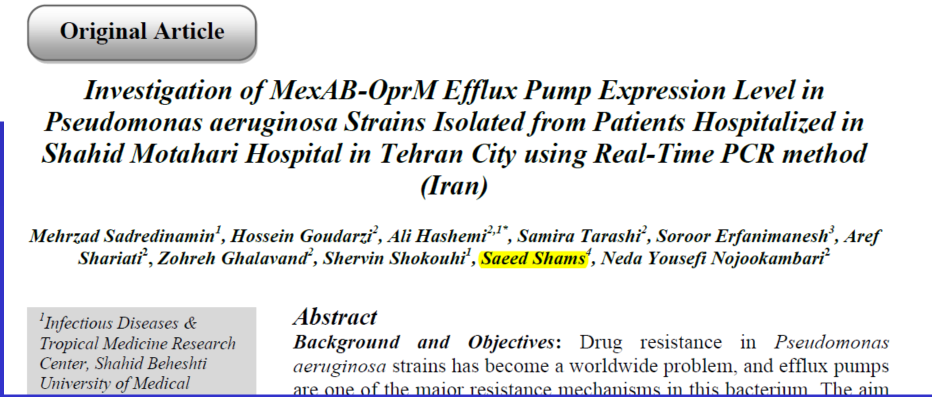

Original Article

Investigation of MexAB-OprM Efflux Pump Expression Level in Pseudomonas aeruginosa Strains Isolated from Patients Hospitalized in Shahid Motahari Hospital in Tehran City using Real-Time PCR method (Iran)

Mehrzad Sadredinamin[1], Hossein Goudarzi[2], Ali Hashemi[2,1*], Samira Tarashi[2], Soroor Erfanimanesh[3], Aref Shariati[2], Zohreh Ghalavand[2], Shervin Shokouhi[1], Saeed Shams[4], Neda Yousefi Nojookambari[2]

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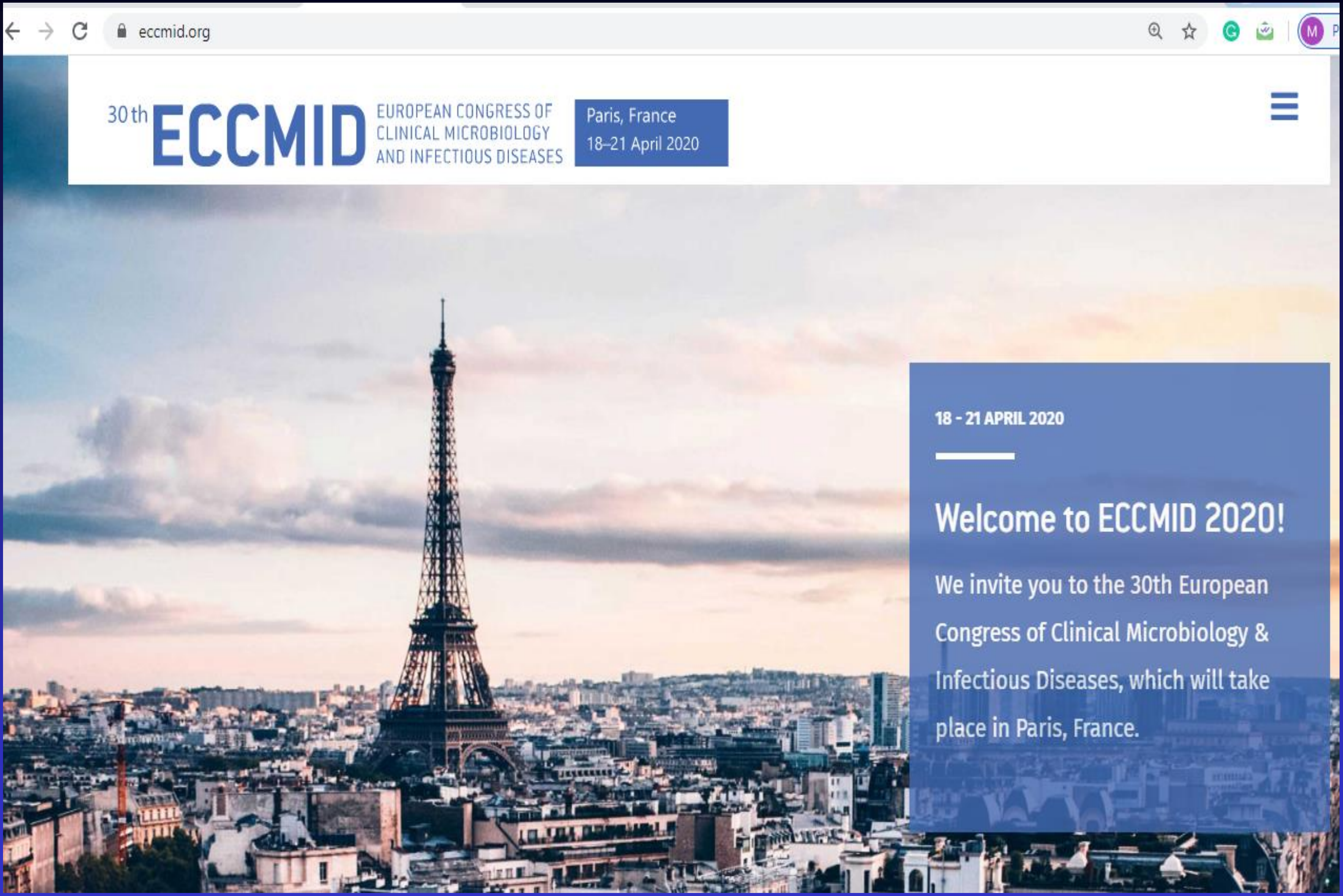
Abstract

Background and Objectives: Drug resistance in *Pseudomonas aeruginosa* strains has become a worldwide problem, and efflux pumps are one of the major resistance mechanisms in this bacterium. The aim



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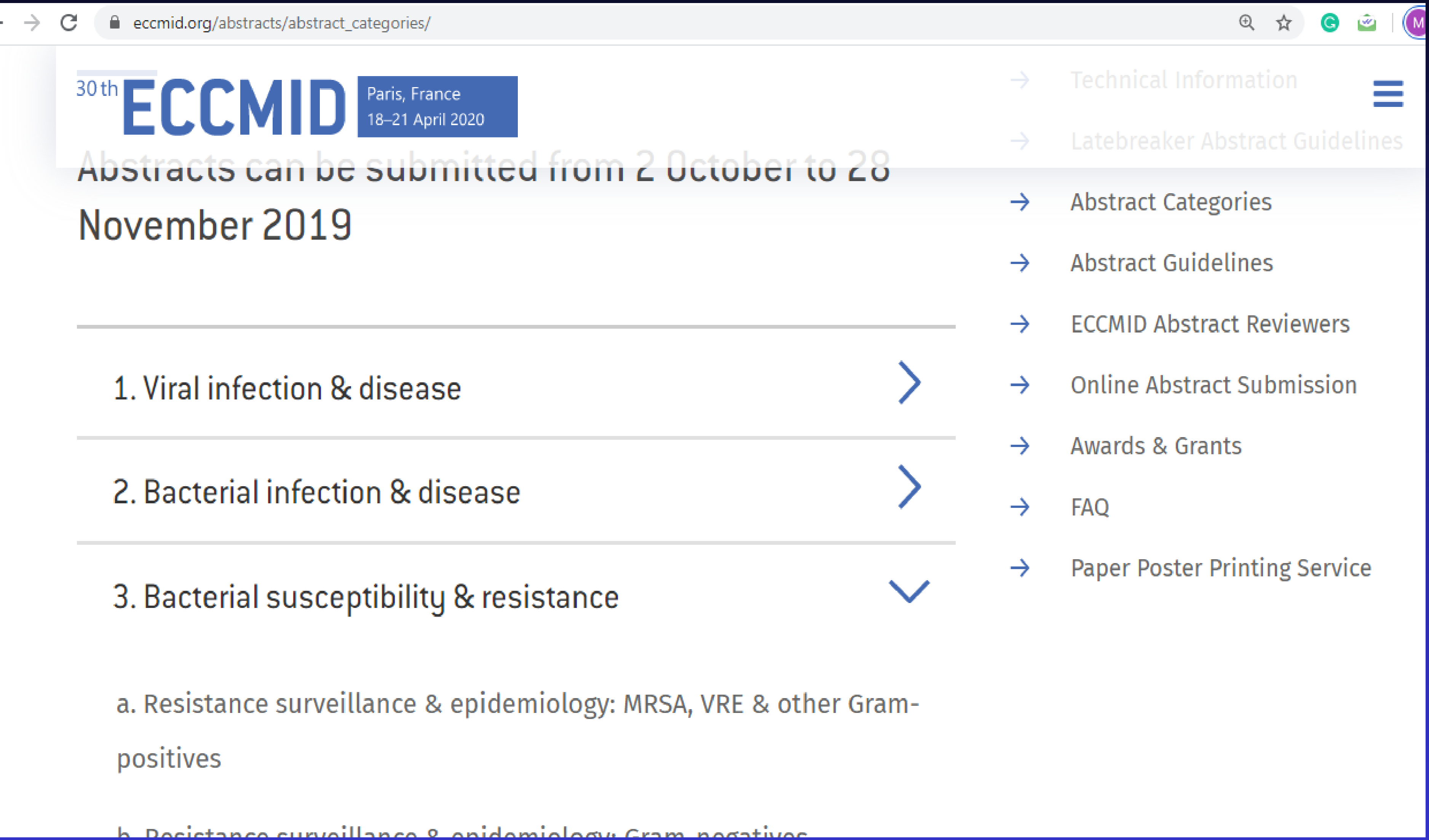
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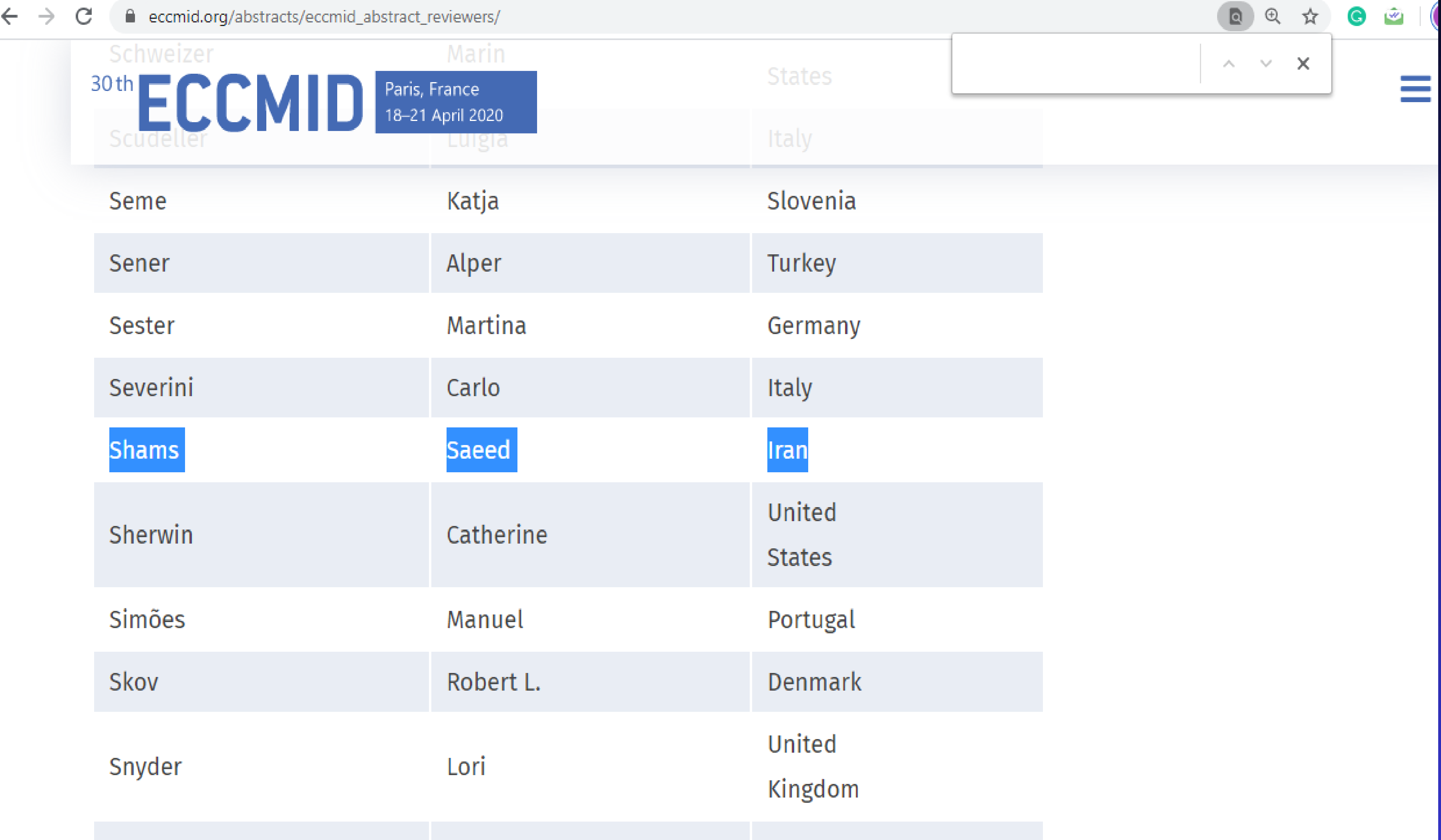

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